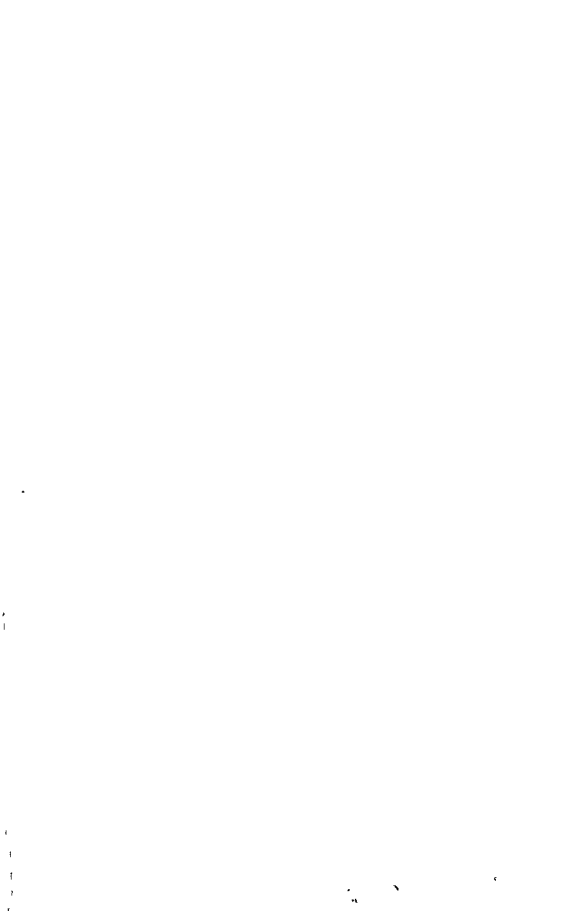


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AN INTRODUCTION
TO
MATERIA MEDICA AND PHARMACOLOGY

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UNIT I

CHAPTER I

OPPORTUNITIES FOR LEARNING PHARMACOLOGY ON THE HOSPITAL WARD

In the care of patients many unique situations arise in which a knowledge of chemistry, physiology and psychology can be applied if the nurse learns to become sensitive to the possibilities in, and importance of, these situations. The interest associated with the recognition and appreciation of opportunities to learn serves as the leavening agent which makes nursing fascinating to both student and graduate nurse. The lack of this appreciation makes each day on a hospital ward something to be lived through, to be grimly endured.

Selection of the instructor to guide students while on the ward will depend upon the teaching plan for the particular ward or hospital. Many times this responsibility is assigned to an already overburdened head nurse. If she has had adequate preparation and has an aptitude for teaching, and if she is sufficiently relieved of house-keeping duties, there probably is no person better able to teach the student pharmacology in all its relations to nursing. In some hospitals someone else, especially interested or better prepared for teaching, may be the one who plans the ward teaching program, in connection with the classroom instructor of pharmacology and the wards and supervises their early experiences in the pouring and passing of medicines. She will be especially interested not only in having the student learn a technic of administering medicines which will make her a safe person to entrust with such a duty, but also in having the student continue to learn something about the medications she is administering and why the patients are receiving them. The classroom teacher does not have as close an association

with patients as does the head nurse or her assistants, but she, too, may render invaluable aid in helping a student in her study of pharmacology.

The classroom instructor, the teaching supervisor, and the head nurse are all persons who have had special preparation in their field and from whom the young nurse can receive expert guidance. Regardless of who carries the major responsibility for the ward teaching of student nurses, the learning must take place within the student; therefore, upon her falls a share of the responsibility for acquiring the knowledge and skill essential for her role in drug therapy. A real student does not wait to be spoon-fed with interesting facts but seeks the satisfaction which comes from the thrill of adventure in learning.

Many of the following points in the observation of drug effects must be gradually and persistently instilled in the minds of young students and will be lost on the inexperienced student unless she reacts to them repeatedly in many different situations. Skill in observation is not an ability with which we are born; it is developed through years of patient and persistent effort.

1. Why are certain drugs prescribed for certain patients? For example—why should one patient be given morphine, another codeine, still another pantopon and possibly another papaverine? All are derivatives or preparations of opium: why should this distinction be made? This is a type of question which a real student will ask himself and for which she will try to find an answer. In addition, every responsible person on the ward should be alert to know what is being done for the patients and why it is being done. It is not sufficient to make certain that Mrs. Brown received her correct dose of mandelic acid at four o'clock; the student giving that medicine should have some concept of why Mrs. Brown was to have that particular medication at that particular time of the day. I have known student nurses to withhold doses of morphine which had been ordered for patients just operated upon because they did not think the medicine necessary since the patient was sleeping. Those students did not understand that the purpose of giving the drug was not only to relieve pain but also to check peristalsis and prevent hemorrhage during the first twenty-four hours after surgery. In another instance, a student was known to be surprised that a cardiac patient did not at once go to sleep after a dose of papaverine, reasoning that since it was a derivative of opium it should produce sleep.

It is true that a nurse is not expected to speculate over theoretical problems of pharmacologic action, but she is expected to observe and record accurately the condition of patients. How can she observe the results of drug action when she does not know which symptoms are likely to be relieved by the medication?

2. Another important item is the expected action of a drug for a particular patient. A postoperative patient with a bad cough may have had ordered a grain of codeine to be given every three hours. Upon having her attention drawn to it, the student may be surprised to find that the only effect she is able to observe is that the patient stops coughing so violently after about the second or possibly the third dose, and even though the drug is derived from opium there are few other reactions which she may have expected, such as drowsiness or a pupillary reaction. Or a student may observe great alertness and restlessness after a dose of morphine. Only by watching the effect of medicines on patients is it possible for a student really to understand that the expected action of a drug is not the one sometimes observed, either because of its specific action or because of a peculiar reaction on the part of the patient.

3. A third item of importance in the learning of pharmacology is the recognition of early symptoms of overdosage. I recall seeing two students help a patient walk down the hall. When they were asked why they were helping this patient who should have been able to walk unassisted, they replied that the patient had developed a stagger and seemed increasingly uncertain on her feet every time she tried to walk. One of these same nurses was giving the patient a dose of sodium bromide twice a day. As soon as this symptom was called to the attention of a physician, the medication was discontinued. These nurses had apparently seen no connection between this developing symptom and a medication which the patient was being given, and, furthermore, they were not conscious of the fact that a patient may exhibit only one or perhaps two symptoms of poisoning instead of a whole list, such as the student may have noted in her materia medica text. Students of pharmacology must learn to note any unusual reaction on the part of patients and see whether any connection may be made with the medications which the patient is receiving. If a nurse is to be of any professional value, she must be able to detect unusual effects of drugs.

4. The interrelation of drug action and the findings recorded on the patient's laboratory reports should become significant to the student. For example, if students are to know the effectiveness of giving iron and liver preparations, they must learn to look to more

objective ways of measuring such effectiveness; namely, the blood reports; likewise, to realize the effectiveness of mandelic acid, they must watch the bacterial culture reports on the urine; to understand the symptoms of toxicity following the administration of a sulfonamide, they must observe the blood cell counts; and to explain the use and effectiveness of vitamin K, they must know the clotting time of the blood.

Granted that interpretation of laboratory findings is outside the realm of the nurses' responsibility; nevertheless, if the student is to administer medicines intelligently, she must think what she is doing and realize that the administration of medicines is based on scientific findings.

5. The channel of drug administration is another topic peculiarly suited to ward study. A student is certain to notice that some drugs like sulfonamides may be given by mouth, intravenously, or by rectum, but she must also seek an understanding of why one channel is preferred to another for individual patients. The ward is also the best place to relearn why tinctures are not given hypodermically, why insulin and adrenalin are not given by mouth, or why a mercurial may be given deeply into a muscle. It is not enough to learn the fact that tinctures are, for the most part, given by mouth; students should understand the reason: namely, that tinctures, being alcoholic preparations, are irritating to tissues.

6. The range of dosage of drugs is gradually learned by considerable repetition in the administration of medicines until only a dull student will fail to recognize and question dosage which deviates markedly from the usual. For this reason a young student should welcome help and supervision if she is to avoid errors of dosage. An inexperienced student should not feel that she is considered untrustworthy when the head nurse, or someone appointed by her, checks the orders for medications.

The form of ward teaching, such as bedside, clinic, seminar, or individual conference, is not as important as the consideration of principles underlying effective study and learning.

One principle is that *students should utilize every opportunity for learning that is afforded by the institution*. There is no place to learn nursing quite like the actual bedside of a patient. Likewise, here can be gathered a wealth of knowledge pertinent to pharmacology. The ward is the final and the best pharmacologic laboratory. When a patient is returned from the operating room with a flushed face and neck, and dilated pupils, and complains of unquenchable thirst, this is an ideal time to learn the early symptoms of atropine poison-

ing. In a relatively short time these symptoms are likely to pass; therefore the time for observation is immediately, even though the patient is observed while being made comfortable just after the return from the operating room.

✓An excellent way to build a concept of bromism is to study such a condition when it presents itself on the ward. Observe the patient who, after receiving a bromide for some time, develops a rash on the face, a foul breath, a mental aloofness, and sometimes an incoordination of muscles when walking, rather than hope to build a clear concept from textbook pictures and oral descriptions, helpful though these may be. The student will do well to follow the guidance of the ward teacher, for she will be on the alert for teaching material which is unique to the ward and cannot be easily duplicated in the classroom or laboratory.

Another principle is that the student should *relate and recall the activities of previous learning to the situation at hand.*

{ Pharmacology obviously does not operate in a state of isolation but rather functions as a part in a broad field of therapeutics. A patient with pneumonia may be given sulfanilamide, the effectiveness of which will depend upon how the drug is able to act under the existing conditions; i.e., virulence of the infection, resistance of the patient, his ability to maintain a high concentration of the drug, etc. Herein, therefore, lies an opportunity to introduce and correlate certain facts of normal physiology, pathology, and bacteriology, as well as pharmacology. Similarly, experiences and principles of psychology learned from other cases can be reviewed and refocussed in many situations in which they are related to drug administration. Students may be taught that a sick person's sense of taste is frequently deranged and that he tends to be highly suggestible when ill, but such knowledge often needs to be relearned and applied at the bedside.

A physician once related an incident concerning a patient who entered a hospital for treatment for tapeworm. The physician was most eager to have the patient receive every consideration, since he had been persuaded to come to the hospital somewhat against his will. Epsom salt was to be given in divided doses, half an hour apart. A nurse took the first dose in to the patient in half a glass of tepid water and left him to swallow it as best he could. A second dose was delivered in a like manner, after which the patient declared he was through and was going home. The physician was called, and he with some difficulty persuaded the patient to stay a little longer. The doctor then asked to see the most intelligent and

objective ways of measuring such effectiveness; namely, the blood reports; likewise, to realize the effectiveness of mandelic acid, they must watch the bacterial culture reports on the urine; to understand the symptoms of toxicity following the administration of a sulfonamide, they must observe the blood cell counts; and to explain the use and effectiveness of vitamin K, they must know the clotting time of the blood.

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ward classes with an air of boredom. One reason may be that the student feels she is well versed in drugs and that there is little left to be learned.

If a unit of ward instruction is planned to meet the needs of a group of young students, the more mature students should not be expected to attend, and vice versa. In some instances the leader of the discussion group will be able to bring the older students into the discussion in such a way that their contribution is enlightening, based on a broader experience than that of their younger associates. A senior student who takes an active part in a discussion of hypnotics as given to the patients on a ward should be able to relate from her experiences with these drugs a broader generalization of their uses than the younger student would be capable of giving. Social implications in the uses of hypnotics as related to particular patients might be a subject the consideration of which would be profitable and interesting to an older student, while the younger nurses are studying the fundamentals of these drugs.

At the present time a great many new drugs are being introduced on the drug market and are being given for a great variety of human illnesses. The more experienced student should assume the responsibility of collecting reliable information concerning these drugs.

It is apparent that in order to become skilled in the care of patients with heart disease a nurse must have cared for many such patients, since no two of them are ever exactly alike. It is equally true that if a nurse is to become skillful in fulfilling her responsibilities as they are related to drug therapy, she must have practice among many patients. The nurse who becomes complacent with the conviction that she knows all about drugs because she has given many, has ceased to learn and thereby limits her professional usefulness.

A fourth principle is that *students should recall and review essential facts whenever an opportunity presents itself*. Since the efficiency of our learning depends so largely upon the opportunity for the use of knowledge and skill and upon the spacing of occasions for exercise, it is reasonable to say that the fundamentals of pharmacology should be systematically reviewed on the ward.

✓ Principles of drug action may be expertly taught in the classroom, but unless students continue to think in terms of such, the original lesson may be almost a total loss. When asked, "What is the action of cascara?" the usual reply is that it is a cathartic, unless students have learned to differentiate the action from the result of action.

best-looking nurse on the floor and laid the difficulty before her, urging her to do her best to gain the cooperation of the patient. She agreed to try. When the next dose of medicine was due, she covered a small tray with a clean napkin and on it placed the solution of Epsom salt to which had been added a liberal amount of chipped ice. On a small plate she placed two neatly cut slices of orange and for a finishing touch a fresh rose. She then carried the tray to the patient's room, placed it on the bedside table, and pleasantly reminded him that his medication was due. She waited for him to take the medicine and in the interval kept up a play of light conversation which served to distract his mind from the taste. He responded to the end that he stayed for the complete treatment. Just what it was that won him over is debatable, but probably the appearance and attitude of the nurse as well as the ice in the medication, and the rose on the tray combined to make an almost pleasant experience of a formerly gruesome one.

A good nurse eventually comes to use a psychologic approach which is to the advantage of both the patient and herself. Such behavior tactics or psychology can be cultivated in any nurse who is desirous of learning them. The amount of transfer of training from the classroom to the bedside of the patient is too often apparently nil, hence the need for students to become aware of the situations in which such applications are needed.

Another way in which the activities of the student can be related to the ward experience is through the effort to apply facts learned in lectures in medical and surgical nursing. An excellent time to study and discuss digitalis on the ward is when the lectures on diseases of the heart are being given in medical nursing. Here the ward teacher will help the student to understand better the relationship between heart disease and one of the forms of treatment. Likewise, a good time to study thyroid extract, pituitary extract, or theelin on the ward is when the lectures on endocrine disorders are being given.

The material studied should be more difficult than that of previous similar experiences, and the student should attempt to learn on a progressively higher level in accordance with her interests and capacities.

One of the problems confronting teachers in schools of nursing is the rather appalling lack of interest on the part of the senior students. We wonder what has happened to the student who at one time sparkled with interest and enthusiasm and who now attends

ward classes with an air of boredom. One reason may be that the student feels she is well versed in drugs and that there is little left to be learned.

If a unit of ward instruction is planned to meet the needs of a group of young students, the more mature students should not be expected to attend, and vice versa. In some instances the leader of the discussion group will be able to bring the older students into the discussion in such a way that their contribution is enlightening, based on a broader experience than that of their younger associates. A senior student who takes an active part in a discussion of hypnotics as given to the patients on a ward should be able to relate from her experiences with these drugs a broader generalization of their uses than the younger student would be capable of giving. Social implications in the uses of hypnotics as related to particular patients might be a subject the consideration of which would be profitable and interesting to an older student, while the younger nurses are studying the fundamentals of these drugs.

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Gradually through repeated effort to understand this difference there should be a better grasp of why one patient with chronic constipation is given mineral oil or bassorin paste, another with generalized edema is given Epsom salt, and still another with recent food poisoning receives castor oil.

There is also a need to understand more thoroughly that the expected action of a drug is modified by the patient's reaction to it, and by the environment in which the drug is to function. The dosage of phenobarbital can vary tremendously, depending upon whether it is used merely to allay the apprehension of a nervous patient or is given to control the severe convulsions of an epileptic. The range of dosage is therefore best learned and reviewed while caring for patients. Because drugs function under conditions in which many factors operate, the learning of the nursing details associated with the administration of medicines becomes infinitely more impressive when the student observes and studies the interrelation of general nursing care and drug action. The necessity for bed rest, balanced fluid intake and output, and suitable diet is readily understood when caring for a patient who is being treated with digitalis. The limitation of fluids for patients receiving mandelic acid should begin to have meaning when the student has the opportunity of observing the whole patient in whom the action of the drug is one factor in his treatment.

Details of drug administration are often vital and must be learned in a variety of conditions. The need and reason for withholding fluids after cough syrups are given, for dissolving urotropin in water before giving it to a patient, or for giving a liberal amount of water with most medications, are examples of points which the student is likely to forget unless she is properly taught and observes the effects frequently. Since cases are never identical, repetition and drill need never become monotonous if the student is fired with a zest for learning.

Students should strive to develop habits, appreciations, and attitudes which are worthy of cultivation. Every sincere teacher of pharmacology attempts to impress upon students the desirability of developing a technique in the giving of medicines which will result in a maximum of safety to the patient. If a student observes that the other nurses adhere to the established routines, she is likely to follow their example; therefore, the wise thing for the student to do is to follow the best example with which she has contact. Certain details of routine may seem irksome, and the student may be inclined to think that she could figure out many short cuts which would be both

time- and labor-saving. It would be advisable for her to consult her head nurse or ward supervisor as to just why a particular method or rule has been established. She may be interested to learn that the regulation has frequently been the outgrowth of years of experience in which it was found that this particular routine proved to be the most workable.

There is a distressing tendency for nurses to become casual in their attitude toward the giving and taking of drugs. In almost every hospital nurses are forbidden to take medicines except under the prescription of a physician. This policy has been established with good reason, and while most nurses respect the ruling, many *feel free to resort to self-medication for a variety of ailments*. Too much cannot be said about this vicious habit of taking drugs, and if our study is to be effective, it must be along preventive lines. The more a nurse learns about drugs and what they can do, the more likely will she develop respect for them and exercise caution in their use.

The student can acquire valuable knowledge in the use of drugs in no place so well as in the ward. The methods of an expert head nurse and a physician of wide experience are more valuable and will help more than any amount of classroom teaching, however sincere and earnest it may be.

CHAPTER II

INTRODUCTION

Materia Medica (L. *materia*, matter, *medical*) is a general term meaning materials of medicine or a study of the materials used in the treatment of the sick. In a more restricted sense it refers to the study of the origin and physical and chemical properties of drugs. The name *pharmacognosy* is sometimes used synonymously with *materia medica*.

Pharmacology (Gr. *pharmakon*, drug; *logos*, science) is also a broad term to include all knowledge of drugs and their actions. It includes pharmacodynamics which is a study of the action of drugs on living tissues. Pharmacology is a science which borrows freely from other sciences such as physiology, physiologic chemistry, bacteriology, and pathology. In the study of pharmacology emphasis is placed on the *action* of drugs, as well as on their absorption and excretion, and fate in the body.

Pharmacy is the science and art of preparing and dispensing drugs for medicinal use. To know pharmacy one must study the properties, preparations, compounding, preserving, and dispensing of medicine.

Therapeutics (Gr. *therapeutikos*, healing, curative, alleviative) is the art and practice of treating disease by any method that relieves pain, restores health, or prolongs life. In the broadest sense it includes all remedial agents and measures which promote the comfort, well-being, the healing or the prolonging of life of the patient.

Pharmacotherapeutics refers to the study of the uses of drugs in the treatment of disease. Only in rather rare instances are drugs used on an *empiric* basis, i.e., when the action of the drug is not clearly substantiated by laboratory methods.

Toxicology (Gr. *toxikon*, poison; *logos*, understanding) deals with the symptoms, diagnosis, treatment, and detection of poisons.

Posology (Gr. *posos*, how much; *logos*, understanding) is the science of dosage.

Drugs are substances used as medicines. The word comes from the Dutch, *droog*, meaning dry. Its use probably comes from the

fact that dried plants at first formed the greatest source of medicines. The terms *drugs* and *medicines* are used interchangeably. They are chemical substances which bring about changes in living protoplasm.

Drugs at present include:

1. Pure chemicals, such as sodium bicarbonate or sodium salicylate.
2. Mineral products, such as petrolatum or ichthyol.
3. Plant parts or products, such as ergot, digitalis, opium, nux vomica, senna, cinchona, or sarsaparilla.
4. Animal products, such as cod-liver oil, cantharides, honey (mel); the waxes—cera flava and cera alba, adrenalin, thyroxin, gelatin, lanolin, heparin, ox bile, lard, etc.
5. Crude drugs are the commercial forms of the natural plant or animal drugs, such as digitalis leaves, nux vomica beans, ergot, cinchona bark, thyroid, etc. They are sometimes used because the active constituent cannot be prepared or because in some cases they may contain more than one active principle as does opium, which in some cases is preferable in the crude form.

Drug Standards

The United States Pharmacopoeia is an authoritative book establishing standards for drugs. The drugs listed in it are said to be "Official" and a drug sold under the name given in the Pharmacopoeia must legally conform to its standards. Drugs marked U. S. P. are guaranteed by the manufacturer to conform to this standard.

A Pharmacopoeia is a necessity because drugs sold under the same name should have the same strength. Before the U. S. P. was published, drugs in different parts of the country were found of different strengths. The first U. S. P. was published in 1820, and it was revised every ten years up to 1936. The present Pharmacopoeia (XIII) became official April 1, 1947. While it has been customary to revise the Pharmacopoeia every ten years, supplements are now printed in the interim which include new preparations. We may expect more frequent revisions. Patented drugs may not be listed in the Pharmacopoeia. Such drugs may eventually be included in the Pharmacopoeia when the patent expires. Insulin is an example of a preparation which could not be included in U. S. P. XI but is included in U. S. P. XIII.

The Pharmacopoeia not only includes a list of approved drugs but it describes and defines them in respect to source, chemistry, physical

properties, tests for identity, method of assay, storing, dosage, and directions for compounding if not a single drug.

Revision of the U. S. P. is in charge of The United States Pharmacopoeial Convention. This is composed of delegates from the Surgeon-General's office of the War Department, Bureau of Medicine and Surgery of the Navy Department, Bureau of Public Health of the Treasury Department, United States Department of Agriculture, Appraisers' Bureau Treasury Department, American Medical Association, American Pharmaceutical Association, American Chemical Society, Association of Official Agricultural Chemists, Association of State and National Food and Dairy Departments, National Wholesale Druggists' Association, National Association of Retail Druggists, National Dental Association, State Medical and Pharmaceutical Societies, and Schools of Medicine and Pharmacy.

The National Formulary (N. F.) is published by the American Pharmaceutical Association, and a new edition appears at the same time or shortly after each new U. S. P. Drugs included in it are marked N. F. It contains the formulas of many common preparations not included in the Pharmacopoeia. Both these books are legal standards of the pure food and drugs act.

New and Nonofficial Remedies (N. N. R.) is a book published every year by the American Medical Association, and contains a description of nonofficial drugs which, according to their Council on Pharmacy and Chemistry, are worthy of trial and are honestly marketed.

A Dispensatory is a general reference book on the botany chemistry, pharmacy and therapeutics of drugs. The United States and the National dispensatories are best known in this country. They are comprehensive and quite reliable. **The United States Dispensatory** is issued by the American Pharmaceutical Association.

Useful Drugs, published by the American Medical Association, presents a brief but practical discussion of the most essential drugs, whose worth has been established.

Trade Names.—Some pharmaceutic concerns market their official drugs under trade names rather than under official names. In order to promote sales under the trade name extensive advertising is usually necessary. This involves considerable expense which is borne mainly by the patient when he buys the drug under the trade name instead of the official title. Below are a list of examples of drugs known by two names, one of which is official and the other is not.

TRADE OR PROPRIETARY NAME	OFFICIAL NAME
Adrenalin	Epinephrine
Aspirin	Acetylsalicylic acid
Atophan	Cinchophen
Eserine	Physostigmine
Hyoscyne	Scopolamine
Hydrogen peroxide	Hydrogen dioxide
Luminal	Phenobarbital
Oil of wintergreen	Methyl salicylate
Theocin	Theophylline

Nonofficial Drugs.—Many of the drugs which are on the market are not official, but they may be promoted by reliable drug companies who through their own laboratories have carried on careful research and who not only are willing to announce the composition of their product but make only cautious and well-substantiated claims for it. As a return for their investment they may patent their product and have exclusive rights for its sale and manufacture.

Not all patented drugs are made by such reliable firms. Too often claims are extravagant and unwarranted and backed up by very meager experimental evidence. Consequently, the busy physician often relies on the judgment of the Council on Pharmacy and Chemistry of the American Medical Association rather than attempt to determine the true merits of many new drugs for himself. Some of the unofficial preparations are, of course, eventually accepted by the Pharmacopoeia Committee as conforming to its standards, and they are then official preparations. Other unofficial preparations may never be accepted by the Pharmacopoeia Committee although they are extensively used.

Both the public and the physician are protected to some extent from the unethical practices of unreliable drug manufacturers by the provisions of the *Federal Food and Cosmetic Act*. This is further described in Chapter XXIV. The law rather rigidly controls the purity, standards, and composition of drugs and drug mixtures.

Standardization of Drugs

Drugs in times past varied a great deal in their strength or activity. It is quite obvious that to secure reliable effects, a drug must be of uniform or nearly uniform strength. Digitalis, for example, varied greatly in its activity depending on where it was grown, the age of the plant, the conditions under which it was harvested, the conditions under which it was preserved, the age of the preparation, etc.

Again, unscrupulous manufacturers of expensive drugs may offer products of low concentration, or products that are adulterated.

For these reasons the U. S. P. demands that drugs be of a certain standard strength. There are two methods of assaying or of standardization:

1. Chemical.
2. Biologic or pharmacologic.

By chemical assay, we mean chemical analysis to determine the ingredients present and their amount. By chemical standardization is meant the making of a definite chemical compound to a known strength. Thus normal, or normal-tenth solutions of acids are standardized solutions.

Opium is known to contain certain alkaloids, but these may vary greatly in different preparations. Consequently the U. S. P. standard demands that opium must contain not less than 9.5 per cent and not more than 10.5 per cent of anhydrous morphine. Opium of a higher morphine content may be reduced to the official standard by admixture with opium of a lower percentage or with certain other rather inert diluents, such as sucrose, lactose, glycyrrhiza, magnesium carbonate, etc.

Chemical standardization is the preferable method, but before a drug can be standardized chemically, we must know:

1. The active chemical ingredients.
2. We must have a method of separating and analyzing them.

There are many drugs of which we either do not know the active ingredient, or we have no available method of analyzing and standardizing it. For these reasons some drugs are assayed by biologic methods—bio-assay. Bio-assay is the determination of the standard dose by the effect on man (clinical assay) or animals.

Bio-assay is performed by determining the amount of preparation required to produce a definite effect on a suitable laboratory animal under certain standard conditions. This is usually done by comparing the action of the drug being assayed with that of a known standard and must be done under carefully controlled conditions.

The method of assay varies with different drugs and their characteristic therapeutic actions. For example, the potency of insulin is measured in relation to its ability to lower the blood sugar of rabbits while that of liver preparations is measured in terms of their potency in patients with pernicious anemia in relapse.*

*Goodman, Louis, and Gilman, Alfred: *The Pharmacological Basis of Therapeutics*, New York, 1941. The Macmillan Company, p. 18

Another way of performing bio-assay is to measure the toxic property of a drug. The strength of digitalis is measured by its ability to slow the heart of the cat.

The strength of a drug which is assayed biologically is usually expressed in units. For example, Cod Liver Oil, U. S. P., must contain at least 850 U. S. P. units of vitamin A and 85 units of vitamin D per gram. Both the unit and method of assay are carefully defined so that national and sometimes international standards exist.

CHAPTER III

PHARMACEUTIC PREPARATIONS

Pharmacy is the art and science of preparing drugs for medicinal use. Pharmaceutical preparations are the forms in which medicines are made ready for use. Official preparations must conform to the formulas and directions in the U. S. P. and N. F. They are made by pharmacists in manufacturing laboratories and to some extent in the retail pharmacy. Different methods of administration demand different preparations of drugs. Crude drugs, especially those of plant origin, are usually ground or finely divided and then subjected to some extracting process which dissolves out their medicinal content. One of the important types of pharmaceutical preparation is the *solution*.

Solutions

Definition of a Solution.—Chemists find difficulty in finding a definition of a solution that answers all objections. A practical definition is: A solution is a homogenous mixture of a substance in a liquid which appears clear in ordinary daylight and which cannot be separated into its constituent parts by ordinary mechanical processes of filtration through paper or by decantation after settling.

In pharmacy the term *liquor* or *true solution* is an aqueous liquid preparation containing one or more substances, usually nonvolatile, completely dissolved. In other words, *a true solution is an aqueous solution of a nonvolatile drug*.

In a solution the molecules of dissolved substance are uniformly distributed; that is, any part of a solution has exactly the same composition as any other part, provided the temperature of all parts is the same. For example, if we place some common salt in a beaker and fill the beaker with water, the salt dissolves and a solution is formed. If, after solution has taken place, we remove equal samples of the mixture from the top, bottom or any part of the beaker and evaporate them to dryness, we will obtain the same amount of salt in each of the samples, showing that the salt was uniformly mixed with the water.

Parts of a Solution.—A solution has two parts: the *solute*, which is the dissolved substance and the solvent, the substance in which it is

dissolved. The solute may be a solid, a liquid or a gas; the solvent is usually a liquid but may be a solid or a gas.

Solubility.—The solubility of a substance is the amount of that substance which will dissolve in a specified solvent. If the latter is not mentioned, water is understood, and as temperature affects solubility, the temperature is usually mentioned for the solution given. If it is not stated, ordinary temperature 25° C. (77° F.) is understood.

Solubility may be expressed in two ways: (1) as the number of grams of solute that will dissolve in 100 cc. of solvent; (2) as the number of parts of the solvent required to dissolve one part of the solute.

Theoretically, no substance is absolutely insoluble but the amount that will dissolve may be so small that for practical purposes the substances are considered insoluble; on the other hand, it may be so great that it exceeds the amount of solvent. A substance that is insoluble in one liquid may dissolve readily in another liquid. Hence, the solubility of any substance depends upon the *nature of the substance* and the *nature of the solvent*. It also depends upon the *temperature of the solvent*. The solubility of most substances is increased by heating; some substances are little affected by temperature; some substances are more soluble in cold water. Thus 100 cc. of water will dissolve 13 grams of potassium nitrate at 0° C. and 246 grams of the same substance at 100° C. At 0° C., 36 grams of sodium chloride will dissolve in 100 cc. of water but only 39 grams will dissolve at 100° C. Calcium hydroxide, on the other hand, is about half as soluble at 100° C. as at 20° C. For gases dissolved in liquids there is but one rule in regard to temperature: increasing the temperature decreases their solubility.

Classification of Solutions

I. Based on Strength of Solution.—The strength of concentration of a solution means the amount of solute it contains. A *dilute* solution is one that contains a small amount of solute. A *concentrated* solution contains a large amount of dissolved substance. When a solvent has dissolved all the solute that it can hold at ordinary temperature, the solution is said to be *saturated*. The saturation point or limit of solubility is expressed in percentage; e.g., a saturated solution of boric acid is 5 per cent in strength. In some solutions no saturation point is possible as there is no limit of solubility of the substances involved. Such substances are said to be miscible in all proportions; examples are alcohol, glycerin, and formalin.

II. Based on Type of Solvent Used.

A. *Water as Solvent.*—

1. **Waters (Aquae)** are solutions (unless otherwise stated) of volatile substances in distilled water. The volatile substance may be solid, liquid, or gaseous. An example of a solution of a solid substance is camphor water; of a gaseous, ammonia water; and of a liquid substance, peppermint water. Waters may be divided into two classes: (1) Aromatic waters whose action is due to flavor and odor. They have no other action. (2) Medicated waters of which ammonia water is a type.

Aromatic waters are the most numerous. They are solutions of an aromatic volatile substance in water.

Chloroform water (*Aqua Chloroformi*) is prepared by adding chloroform to water and shaking the mixture. The excess falls to the bottom and keeps the water saturated. When used the saturated clear fluid is poured from the top.

Camphor water (*Aqua Camphorae*) may be prepared in a similar manner.

Aromatic waters are used for flavor only. There is not enough oil in them to have any other effect. They do not keep well and should be rather fresh when prescribed.

Medicated waters, such as ammonia water, contain a definite amount or percentage of the drug named.

2. **Syrups (Syrupi)** are aqueous solutions of a sugar. Simple syrup is an aqueous solution of sucrose (85 per cent). Syrups are frequently used as a vehicle to sweeten some active agent. Among the syrups commonly used are Syrup of Raspberry, Syrup of Cherry, Syrup of Cinnamon, and Syrup of Licorice. These are all N.F. preparations except syrup of licorice.

3. **Mucilages (Mucilagines)** are aqueous preparations containing viscid substances like gums; starches, and similar colloid bodies. From a strictly physical point of view, mucilages should probably not be grouped with solutions. They are colloidal solutions or suspensions.

Mucilages are used mostly to lessen the taste of drugs, or to protect a surface from irritation. By this action they may also lessen vomiting after a medicine. Mucilage of acacia is also used intravenously after hemorrhage, because it is inert and remains in the vessels longer than physiologic salt solution. All mucilages should be freshly prepared, since they mold and spoil quickly. They are

inert bodies. may be used ad libitum internally, as vehicles. Tragacanth is used externally as a protective.

The two most important mucilages are Mucilage of Acacia which is liquid and Mucilage of Tragacanth which is a jelly. Both are listed in U. S. P.

B. Alcohol as Solvent.—

1. The solution of a nonvolatile substance in alcohol is known as an alcoholic solution.

2. **Spirits (Spiritus)** are alcoholic solutions of a volatile substance. They are popularly known as essences. As in aquae, the dissolved substance may be solid, liquid, or gaseous. They differ from waters therefore in the solvent used and also in the strength.

Most spirits contain from 5 to 10 per cent or even 20 per cent of the active drug.

The advantage of these preparations is that alcohol is a preservative. A disadvantage is that alcohol has a pharmacologic action which in some cases may be undesirable. Some examples of spirits are: Spirit of Camphor, Spirit of Peppermint, and Spirit of Nitrous Ether.

3. **Elixirs (Elixira)** are aromatic, sweetened spirituous preparations, frequently used as flavors and adjuvants, and sometimes contain active medicinal substances. The word *elixir* is of Arabic origin and was applied to a much sought remedy that would sustain life indefinitely—The Elixir Vitae. The term was also synonymous with Philosopher's Stone, i.e., something that would turn all base metals into gold.

Although elixirs are much used and one may prepare an elixir of any drug, there are only two listed in the U. S. P., namely, Aromatic Elixir and Elixir of Phenobarbital, although the National Formulary contains a large number of elixirs.

C. Glycerin as Solvent.—

Glycerites (Glycerita), U. S. P., are solutions of medicinal substances in glycerin. They are used on mucous membranes when continuous medication is desired. Because of the adhesive property of the glycerin, they are retained longer than water solutions and are less irritating than alcoholic solutions. Glycerites keep well. The most important U. S. P. preparations are Glycerite of Tannic Acid, Glycerite of Starch, and Glycerite of Boroglycerin.

D. Oleic Acid as Solvent.—

An oleate (oleatum) is a solution of a drug in oleic acid. Oleic acid is absorbable by the skin, and when substances are dissolved in it they enter the circulation more readily than in other solvents. The most important is the oleate of mercury (Oleatum Hydrargyri). This contains 25 per cent of yellow mercuric oxide.

E. Ether and Alcohol or Acetone as Solvents.—

Collodions (Collodia) are solutions of pyroxylin (guncotton) in mixtures of ether and alcohol, or of acetone. Collodion is *very inflammable* and should be kept away from a flame.

Flexible collodion is a mixture of Canada balsam, castor oil, and collodion in the above-named solvents.

A collodion is intended for application to the skin as a protective covering for minor wounds. The solvents evaporate and leave a film which adheres to the skin. Flexible collodion is used especially over joints or moving parts.

III. Solutions Based on Method of Extraction.

1. **Infusions (Infusa)** are solutions of vegetable principles obtained by soaking the drug in hot or cold water, but it is not kept boiling. The time of infusion may be specified. Old, dry vegetable material requires a longer time than fresh material. The strength also may differ. If the strength is not specified, moisten 50 grams of the drug with 50 cc. of cold, distilled water and allow it to stand 15 minutes. Then add 900 cc. of boiling distilled water, cover tightly and allow it to stand for an hour, then filter and make to 1,000 cc., or a 5 per cent infusion.

The concentrated infusions are made with 25 per cent alcohol, and the dose of most of them is 2-4 cc. (30-60 minims).

The other infusions are mostly 5 per cent in strength, and the dose is 15-30 cc. ($\frac{1}{2}$ -1 oz.).

Infusions are sometimes used when it is desired to avoid alcohol in a preparation. *Infusion Digitalis*, N. F., is an often used preparation to avoid the alcohol of the tincture. It is the most important medicinal infusion.

2. **Decoctions (Decocta)** are solutions of vegetable drugs prepared by boiling the drug in water for fifteen minutes and straining. They are 5 per cent in strength except when otherwise stated. Decoction is preferable to infusion with roots, barks, and substances difficult to extract. There are no official decoctions.

3. **Tinctures (Tincturae)** are solutions of medicinal substances in alcohol usually obtained by extraction of vegetable drugs. They contain both volatile and nonvolatile substances but the latter are the most important. An exception to this definition is found in tincture of iodine which is a volatile solid, but the addition of potassium iodide brings it practically within the definition. Tincture of ferric chloride is also a solution of an inorganic substance.

The tinctures of potent drugs represent 10 Gm. of the drug in 100 cc., with the exception of tincture of iodine which contains 7 Gm. of iodine in 100 cc. Tinctures of less potent drugs vary in strength but the greater number represent 20 Gm. of the drug in 100 cc. The tinctures of ferric chloride, tolu, and iodine are not true tinctures, but solutions of these drugs in alcohol.

The dose of a potent tincture is about ten minims. Tincture of Digitalis, Tincture of Hyoscyamus, and Tincture of Opium are examples of official tinctures.

4. A **fluidextract (fluidextractum)** is an alcoholic liquid extract, made by percolation, so that 1 cc. of the fluidextract represents 1 Gm. of the drug. Fluidextracts are the most concentrated fluid preparations, being 100 per cent in strength. They have the advantage over tinctures because of the smaller dose and a smaller alcoholic content.

Since many of them precipitate in the light, they should be kept in dark bottles and they should not be used if much precipitate is present. Fluidextract of Cascara Sagrada, Fluidextract of Ergot, and Fluidextract of Glycyrrhiza are examples of official fluidextracts.

5. A **wine (vinum)** is a tincture in which wine is used as the menstruum to improve the taste. None is listed in the U. S. P.

6. **Extracts (Extracta)** are solid or semisolid preparations of the drug prepared by percolation of the drug and evaporation of the percolate. The menstruum employed in the extraction varies and may be alcoholic, hydroalcoholic, aqueous, alcoholic and alkaline, or alcoholic and acid. Extracts vary in strength from 2 to 13 times as strong as the drug from which they are made, but many extracts are from 4 to 10 times as strong as the drug. Most of them are 4 times the strength of a fluidextract. Extracts are made in three forms: semiliquids or those of syrupy consistency, plastic masses, or pilular extracts, and dry powders known as powdered extracts.

The dose of an extract is usually about $\frac{1}{4}$ of a grain, although the dosage does vary. Extract of Belladonna, Extract of Cascara Sagrada, and Extract of Liver are examples of official extracts.

Mixtures

In a broad sense mixtures are a combination of two or more substances which can be separated by physical means, that is, they are not chemically united. **Pharmaceutic mixtures** are preparations of insoluble drugs in water which are usually held in suspension by the aid of a gum or some other viscid substance. Such preparations are often more easily swallowed by patients than is the drug in dry form. An example of an official mixture is Chalk Mixture which contains 20 per cent of compound chalk powder (chalk, 20 Gm.; sucrose, 50 Gm.; acacia, 20 Gm.) flavored with cinnamon water.

Suspensions

Suspensions are mixtures which for a time appear homogeneous but after a time the ingredients separate.

Milks (Magmae) are bulky suspensions in water of insoluble preparations resembling milk or cream. They are closely related to the pharmaceutic preparation called a mixture, but are more gelatinous. Milk of Magnesia, which contains between 7 and 8.5 per cent of magnesium hydroxide, is a good example of a milk.

Emulsions (Emulsa) are suspensions of fats or oils in water by the aid of an emulsifying agent. Gum acacia is the agent most frequently used. When well made an emulsion should keep its homogeneity for six months or longer. Emulsion of Cod Liver Oil and Liquid Petrolatum are in the U. S. P.

Liniments (Linamenta) (<lino, to smear) are mixtures of drugs with oil, soap, water or alcohol and are intended for external application only. They are usually applied by rubbing.

The oil and the soap of liniments adhere to the skin and serve as lubricants in rubbing. Many of the ingredients in a liniment are volatile, and after rubbing the skin with it, the skin is covered to prevent further evaporation and to keep it warm. They relieve pain or swelling by counterirritation, and by improving the circulation.

The liniments of camphor and of chloroform are the most used.

Most liniments are anodynes and rubefacients; that is, they relieve pain and cause a reddening of the skin surface where they are applied.

Lotions (Lotiones) are usually aqueous preparations containing suspended matter and are intended for washes or soothing local applications. Many lotions are patted on the skin rather than

rubbed on. White Lotion (*Lotio Alba*), N. F., contains 4 per cent zinc sulfate and 4 per cent potassium sulfide. Calamine lotion (*Lotio Calaminae*), U. S. P., contains calamine 8 per cent, zinc oxide 8 per cent, and glycerin 2 per cent, in limewater. The U. S. P. lists also Benzyl Benzoate lotion. Lotions are protective, emollient, cooling, cleansing, astringent, or antipruritic.

Powders (Pulveres).—Pharmaceutic powders are finely divided solid drugs, or mixtures of drugs. The term *powder* is also applied to single dose quantities of a drug or mixture of drugs in powdered form wrapped separately in powder papers. When given for internal use, powders may be dispensed in folded papers (*chartulae*), in gelatin capsules, or rice flour wafers (disks, *cachets*, or *konseals*). These are usually softened in water before swallowing.

Effervescing powders: to form these the drug is usually mixed in the dry state with sodium bicarbonate and tartaric or citric acid. The effervescence is caused by the reaction of sodium bicarbonate with the acid when mixed with water. Effervescing powders are more pleasant to take, because the carbon dioxide which is liberated is slightly stimulating to the stomach and at the same time carbon dioxide is somewhat of an anesthetic to the nerves of taste, and covers any disagreeable taste the drug may have. Compound Effervescent Powder (*Seidlitz Powders*) is an example of an official powder.

Tablets (Tabellae) are preparations made by compressing a powdered drug into a suitable mold. The powder is usually moistened with alcohol or some volatile liquid to form a wet mass which is easily molded. This makes a preparation that disintegrates easily in the body. Many drugs, such as aspirin, morphine, etc., are available in the form of tablets. When placed in water tablets should disintegrate in a few minutes with not more than gentle agitation. When dry they should crush to a powder without difficulty and at the same time should not wear away at the edges when subjected to ordinary handling.

Pills (Pilulae).—The word pill comes from *pila* which means a ball, although a pill as a pharmaceutic preparation is a mixture of a drug or drugs with some inert material which is cohesive. The mass is molded into globular, oval, or flattened solid bodies convenient for swallowing. A very large pill is called a *bolus* and a very small one a *granule*; a flat pill for use mainly in throat medication is called a *troche* or *lozenge*.

If the active ingredient is very small, a diluent is usually added. Starch, powdered glycyrrhiza, kaolin, and powdered althea are the

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Amytal
 $\frac{3}{4}$ & $1\frac{1}{2}$ grains
tablets
capsule



Ephedrine
sulphate
 $\frac{3}{4}$ grain
capsule



Digitalis
 $1\frac{1}{2}$ grains
powdered
leaf



Sandal wood
5 minims
Oil in gelatin
globule



Creosote
carbonate
5 minims
gelatin glob.



HgCl₂
Bichloride
of mercury
 $7\frac{1}{2}$ grains
(antiseptic)



Cascara
sagrada
extract
3 grains



Potassium
permangan-
ate
5 grains



3 gr.
Quinine
sulphate
chocolate
coated.



Biniodide
of mercury
HgI₂
 $\frac{1}{15}$ grain



Thyroid
extract
2 grains



Bland's
pill
gelatin
coated



Sulphur
tablet
5 grains



Ergot
compound
1 grain



Mercury
& chalk
 $\frac{1}{2}$ grain

diluents commonly used. The cohesive varies with the nature of the basic ingredients. Glycerite of starch, liquid glucose, and extract of gentian are useful for this purpose. The presence of the diluent or the cohesive substance often explains why pills are unsuitable for parenteral administration; the diluent or cohesive may be insoluble or relatively insoluble substances.

Pill coating is done to disguise the taste or improve the keeping qualities of the pills. Pills may be coated with gelatin, tolu, of mixtures of sucrose or lactose, and powdered acacia.

Enteric coating consists of surrounding the pill with some material which is insoluble in the stomach but will be soluble in the intestine. Such coatings may be made of gelatin, stearic acid, keratin, or phenyl salicylate.

Capsules (Capsulae). Another way to prevent irritation in the stomach or digestion of the medication is to inclose the medicine in a gelatin capsule. These may be hard or soft in consistency.

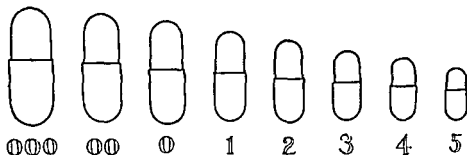


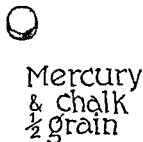
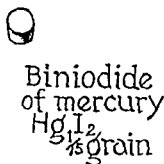
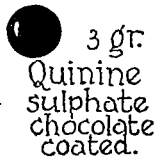
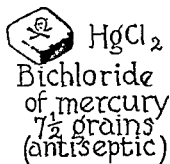
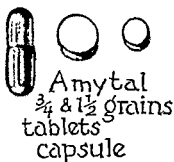
FIG. 1.—Various sizes and numbers of gelatin capsules, actual size. (From Jackson: *Experimental Pharmacology and Materia Medica*.)

Enteric capsules are those that have been coated with an indigestible substance like salol or stearic acid, or made of a substance that will not digest in the stomach but will digest and liberate the drug in the intestine.

As a rule pills should always be fresh. If exposed to the air for a time even the coated ones become hard and may pass through the digestive tract unchanged.

Suppositories (Suppositoria) are mixtures of drugs with some firm base which can then be moulded into a shape suitable for insertion

Plate I.—Capsules, tablets, and globules in natural sizes and colors as they appear on the market at the present time. Note the shape of the Bland's pill and the bichloride of mercury tablet. Special processes are required to make (from two large sheets of gelatin) the globules containing the sandalwood oil and the creosote carbonate. (Samples kindly supplied by Kotte's pharmacy.) (From Jackson: *Experimental Pharmacology and Materia Medica*.)



The heat induces a hyperemia which is believed to influence also the circulation of the deeper or underlying parts. Poultices may be used also to apply counterirritant drugs. If applied too long, poultices cause relaxation and flabby condition of the skin.

Poultices may be made in the household from flaxseed, bread and milk, etc., which are perhaps as effective as any. For this and other reasons, poultices have been dropped from the Pharmacopoeia.

Nebulae Sprays.—These preparations consist of light liquid petrolatum in which are dissolved various aromatics and other medicaments. Liquid petrolatum containing 1 per cent each of menthol and eucalyptol is a common prescription. Nebulae are employed in atomizers for carrying the medicaments into the nose, throat, and trachea.

Plasters (Emplastra) are solid preparations for external use and serve either as simple adhesives or as counterirritants. When applied to the body, the heat softens them and makes them adhere. The base is usually a rubber mixture called rubber plaster.

Adhesive Plaster (*Emplastrum Adhaesivum*), U. S. P. (*Emplastrum Elasticum*), U. S. P. IX.—Mixture of rubber, resins, waxes, and absorbent powder (ZnO, starch, etc.) spread on cotton cloth. Protective. (1.5 Gm. of the plaster mass per 100 sq. cm.)

Sterile adhesive plaster, U. S. P., is also available.

Incompatibility of Drugs

Incompatibility may be defined as that relation between drugs which upon their combination or admixture produces an undesirable change in their chemical nature, physical characters, or the therapeutic value of the resulting compound. Briefly, drugs are incompatible when there is a chemical, physical, or therapeutic reason for not prescribing them together.

Chemical Incompatibility involves a chemical reaction between the ingredients.

GENERAL PRINCIPLES OF THE INCOMPATIBILITY OF DRUGS.—

1. In general, it may be stated that, whenever two soluble substances by direct combination or interchange of radicals are capable of producing an insoluble or

Plate II—Tablets a market at the present (empty) capsules. The the amount (dose) wh cess volume may be m tablets which are inte drug (e.g., aspirin) or acacia. (From Jackso...



HI

Protiodide
of mercury
 $\frac{1}{6}$ grain



Pilulae
ferri
carbonatis
dose 3 pills



Dover
powder
tablet
Dose 5 grs.



Ovarian
substance
whole ovary
5 grains



Blaud's
pill sugar
coated
10 grains



Ichthyol
3 grains



Creosote
chocolate
coated
1 grain



$\frac{1}{30}$ gr.

Strychnine
sulphate
chocolate
coated



Asafoetida
gelatin
coated
2 grains



Methyl-
ene blue
compound
tablet



Atophan
5 grains
in paper
casing



$\frac{1}{200}$ Gr.

Aconitine
gelatin
coated
granule



$1\frac{1}{2}$ gr.
Nembutal
white powder
in yellow
capsule



Veronal
checked
tablet
5 grains



Colored
capsules

less soluble compound, the mixing of their solutions will cause precipitation. Therefore, in combining soluble salts with each other or with infusions, be careful to see that an insoluble precipitate is not unintentionally formed. The precipitation of quinine acetate upon the addition of potassium acetate to an acid solution of quinine, and the precipitation of glycyrrhizin when fluidextract of licorice is added to the same kind of solution, are examples of this class.

2. As a rule, a drug is incompatible with its antidotes and its chemical tests, especially if the latter depend upon the forming of an insoluble precipitate.

3. Mineral acids, especially when concentrated, will displace from their combinations the weaker acids. They also form ethers with alcoholic preparations.

4. The alkalies and their carbonates decompose metallic salts, generally with the formation of a precipitate. The fixed alkalies also liberate ammonia from its combinations and decompose chloral hydrate with separation of chloroform.

5. Strong mineral acids, chlorine water, potassium chlorate, chlorinated lime and solution of chlorinated soda will liberate iodine from the soluble iodides, syrup iodine of iron and syrup of hydriodic acid.

6. Alkaloids are liberated from their combinations by the alkalies and their carbonates; they form insoluble compounds with tannic acid, iodine and iodides; they may be destroyed by chlorinous compounds.

7. The glucosides, such as salicin, santonin and colocynthin, are decomposed by free acids or emulsin.

8. Tannic acid is incompatible with alkaloidal solutions, metallic salts, gelatin, and albumin.

9. Alkalies are incompatible with acids and as a rule modify the action of the cathartic resins due to the formation of resin soaps.

10. A change in the solvent power of the menstruum contained in fluidextracts or tinctures will cause precipitation: (1) of resinous or oily matter when the alcoholic strength is reduced by the addition of water; (2) of gum, mucilage, and albuminous matter if the alcoholic strength is increased.

11. Pepsin is incompatible with alkalies and the metallic salts generally.

12. Gold and silver salts, corrosive sublimate, and potassium permanganate are decomposed by contact with organic matter.

13. Carbonates added to acidulous mixtures or to a mixture of borax and glycerin evolve carbon dioxide which may cause an explosion when in a tightly closed container.

14. Mixtures of energetic oxidizing agents with substances readily oxidized are explosive, more especially when in the dry state; thus, strong nitric acid, chromic acid, oxide of silver, potassium bichromate, potassium permanganate and potassium chlorate may become explosive when mixed with dry organic substances as sugar, tannin, etc., or with glycerin, carbolic acid, alcohols, ethers, oils, sulfur, sulfides, phosphorus, hypophosphites, etc. Nitrate of silver with creosote has caused explosion, and tincture of iodine with ammonia precipitates the highly explosive iodide of nitrogen. (Modified from Coulter: Pharmacology of the Medicinal Agents in Common Use, Eli Lilly & Co.)

Physical Incompatibility is a change in the physical state of one or more of the ingredients of a prescription, such as precipitation, liquefaction, etc.

(a) Alcohol in sufficient concentration precipitates gums, albumin, and many inorganic salts from their aqueous solutions.

(b) Chloral hydrate when triturated in the dry state with camphor, phenol, and some other substances, forms a liquid.

Pharmaceutic Incompatibility occurs when either a chemical or physical change takes place, which, while not affecting the medicinal properties of the prescription, renders it unsightly, nauseous, or otherwise undesirable.

It is impossible to separate pharmaceutic from physical or chemical incompatibility. It may be considered either one or both of these conditions. Resin preparations are insoluble in water, therefore may not mix with it. Most tinctures contain resin and are, therefore, incompatible with water. Mucilages are precipitated with alcohol. In general, spirits, fluidextracts, or tinctures, if diluted to avoid incompatibility, an elixir, spirit or alcohol should be used as the diluent.

Therapeutic incompatibility occurs when the pharmacologic action of the ingredients is antagonistic, as atropine and pilocarpine, an hypnotic and a stimulant in the same preparation.

The following drugs are so generally incompatible that they should be prescribed alone:

Strong mineral acids	Nitrate of silver
Strong alkalies	Potassium permanganate
Alkaloids	Potassium iodide
Arsenic	Salts of metals
Bichloride of mercury	Tannic acid
Lead acetate	

Questions for Review

1. What is meant by an aqueous solution of a drug? Why is it important to designate when ordering a drug from the pharmacy whether an aqueous or alcoholic solution of the drug is desired?
2. What is the difference between a spirit and an elixir?
3. What common beverage is an example of an infusion?
4. Why is it that tinctures should not be given hypodermically?
5. What is the usual difference between a tincture and a spirit?
6. What is an extract? A fluidextract?
7. Why is the dosage of an extract usually less than the dosage of a fluidextract?
8. What advantage does the capsule containing the drug have over the pill or tablet form of medication?
9. What type of base may be used in making suppositories?
10. Why are these preparations usually kept in the ice box?
11. How are they usually administered?

12. What is the official name for an ointment? A plaster?
13. What is meant by incompatibility?
14. Why is physiologic saline solution sometimes used to irrigate the eyes after the use of silver nitrate?
15. How would you take care of a patient's request for a glass of soda water if there was only a short time before she would be given hydrochloric acid with her meal?
16. Why would tea never be given shortly before or after the administration of tincture of iron chloride?
17. Why is bichloride of mercury a poor disinfectant to use for sputum cups, urine, or fecal discharges?
18. What changes in physical properties of a medicine would cause you to discard it from a medicine chest?
19. Of what value is standardization of drugs in therapeutics?

CHAPTER IV

ARITHMETIC REVIEW

Arabic and Roman Numerals

There are two systems of expressing numbers in use in prescription writing, namely, the Arabic and the Roman. The Arabic system uses the figures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. The Roman system uses certain capital letters as follows:

I = 1	X = 10	C = 100	M = 1000
V = 5	L = 50	D = 500	

Roman numbers are expressed by combining the numerals in accordance with the following rules:

1. Repeating a numeral repeats its value: i.e., II = 2; XX = 20; CC = 200. But since doubling V, L, or D would give the equivalent of X, C and M, respectively, these quantities are not doubled.

2. A numeral placed before a numeral of higher value is subtracted from the latter. i.e., IV = 5 - 1 or 4; IX = 10 - 1 or 9; XL = 40; XC = 90; CM = 900. Only one numeral can be so subtracted.

3. Numerals placed after a numeral of higher value are added to the latter: i.e., VI = 5 + 1 or 6; XII = 10 + 2 or 12; LXV = 65; CXXIV = 124.

4. A numeral placed between two higher numerals is always read in connection with the one following: i.e., XIV = 14; XXIX = 29; LIX = 59.

Common Fractions

A common fraction is one or more of the equal parts of a unit. It is expressed by two numbers called the numerator and the denominator. The denominator of a fraction is the number of equal parts into which the unit is divided. The numerator is the number of equal parts taken. The numerator and denominator are called the *terms* of the fraction. A *proper fraction* is one whose numerator is less than its denominator: as, $\frac{3}{4}$, $\frac{5}{8}$, $\frac{2}{3}$. An *improper fraction* is one whose numerator is equal to or greater than the denominator as, $\frac{5}{4}$, $\frac{6}{5}$, $\frac{9}{4}$. A *complex fraction* is one whose numerator or denominator or both are fractions: as, $\frac{\frac{2}{3}}{3}$, $\frac{5}{\frac{1}{2}}$, $\frac{\frac{1}{4}}{\frac{1}{8}}$. A *mixed number* is an integer or whole number and a fraction united: as $4\frac{1}{4}$, $16\frac{3}{4}$.

To reduce a common fraction to its *lowest terms*, divide both terms of the fraction by the greatest number which will exactly divide each term: $\frac{63 \div 21}{84 \div 21} = \frac{3}{4}$. The division of both terms of a fraction by the same number does not change its value.

To raise a common fraction to *higher terms*, multiply both terms of the fraction by the same number. This does not change its value:

$$\frac{5 \times 4}{6 \times 4} = \frac{20}{24}.$$

When several fractions have the same denominator, they have a *Common Denominator*. To reduce fractions to equivalent fractions with a least common denominator, it is necessary first to find the least common denominator, or the smallest number which will contain both of them. For example, to find the least common denominator of $\frac{3}{4}$, $\frac{5}{6}$ and $\frac{7}{12}$ it is necessary to find the smallest number that will contain 4, 6 and 12. This may be done as follows:

$$\begin{aligned} 4 &= 2 \times 2 \\ 6 &= 2 \times 3 \\ 12 &= 2 \times 2 \times 3 \\ 2 \times 2 \times 3 &= 12 \end{aligned}$$

The denominators are resolved into their prime factors, each factor is taken the greatest number of times it is found in any of the numbers, and the factors thus selected are multiplied together. The product is the least common denominator (L.C.D.).

Now, to reduce fractions to equivalent fractions with a *least common denominator*, divide the least common denominator by the denominator of each fraction, and multiply both terms of the fraction by the quotient. For example, to reduce $\frac{3}{4}$, $\frac{5}{6}$, $\frac{7}{12}$ to 12ths, divide 12 by the denominator of each fraction, and multiply both terms of the fractions by the quotients thus obtained: i.e.,

$$12 \div 4 = 3; \quad \frac{3 \times 3}{3 \times 4} = \frac{9}{12}$$

$$12 \div 6 = 2; \quad \frac{2 \times 5}{2 \times 6} = \frac{10}{12}$$

$$12 \div 12 = 1; \quad \frac{1 \times 7}{1 \times 12} = \frac{7}{12}$$

To add common fractions: Reduce the fractions to equivalent fractions with a common denominator, add the numerators of the new fractions, and under the sum write the common denominator:

$$\frac{1}{2} + \frac{2}{3} + \frac{3}{4} + \frac{5}{6} + \frac{7}{8} = \frac{12}{24} + \frac{16}{24} + \frac{18}{24} + \frac{20}{24} + \frac{21}{24} = \frac{87}{24} \text{ or } 3\frac{15}{24} = 3\frac{5}{8} \text{ Ans.}$$

To subtract common fractions: Reduce the fractions to equivalent fractions with a common denominator, subtract the numerator of the subtrahend from the numerator of the minuend, and under the difference write the common denominator:

$$\frac{5}{8} - \frac{1}{4} = \frac{5}{8} - \frac{2}{8} = \frac{3}{8} \text{ Ans.}$$

Multiplication of Common Fractions

To multiply a fraction by an integer or whole number, multiply the numerator:

$$5 \times \frac{2}{5} = \frac{5 \times 2}{5} = \frac{10}{5} = 2 \text{ Ans.}$$

To multiply a fraction by another fraction: Multiply the numerators together and also the denominators and reduce the resulting fraction to its lowest terms:

$$\frac{2}{3} \times \frac{3}{4} = \frac{6}{12} = \frac{1}{2} \text{ Ans.}$$

In multiplying several fractions together, the process may be shortened by canceling common factors before multiplying:

$$\frac{1}{2} \times \frac{2}{3} \times \frac{3}{5} \times \frac{1}{4} \times \frac{4}{7} = \frac{1}{35} \text{ Ans.}$$

Division of Common Fractions

It must be understood that the denominator of the integer is 1.

To divide a fraction by an integer, divide the numerator:

$$\frac{7}{11} \div 7 = \frac{7 \div 7}{11} = \frac{1}{11} \text{ or invert the terms of the divisor and multiply as } \frac{7}{11} \div \frac{7}{1} = \frac{7}{11} \times \frac{1}{7} = \frac{1}{11} \text{ Ans.}$$

To divide a fraction by a fraction: Invert the terms of the divisor, and then proceed as in multiplication:

$$\frac{2}{3} \div \frac{1}{2} = \frac{2}{3} \times \frac{2}{1} = \frac{4}{3} = 1\frac{1}{3} \text{ Ans.}$$

Exercises in Common Fractions

1. Reduce the following fractions to their lowest terms:

$$\begin{aligned} \text{(a)} \quad & \frac{27}{72}, \text{ (b)} \quad \frac{60}{96}, \text{ (c)} \quad \frac{121}{132}, \text{ (d)} \quad \frac{84}{108}, \text{ (e)} \quad \frac{26}{117}, \text{ (f)} \quad \frac{56}{126}, \text{ (g)} \quad \frac{39}{91} \\ \text{(h)} \quad & \frac{156}{169}, \text{ (i)} \quad \frac{63}{70}, \text{ (j)} \quad \frac{75}{125} \end{aligned}$$

2. Write the following improper fractions as mixed numbers:

$$(a) \frac{85}{12}, (b) \frac{63}{8}, (c) \frac{91}{11}, (d) \frac{17}{3}, (e) \frac{160}{13}, (f) \frac{327}{9}, (g) \frac{273}{26}$$

$$(h) \frac{520}{35}, (i) \frac{365}{20}, (j) \frac{175}{4}$$

3. Change the following mixed numbers to fractions:

$$(a) 2\frac{7}{8}, (b) 3\frac{2}{3}, (c) 4\frac{3}{4}, (d) 5\frac{1}{2}, (e) 6\frac{1}{6}, (f) 7\frac{2}{11}, (g) 8\frac{1}{6}, (h) 9\frac{1}{6},$$

$$(i) 16\frac{5}{8}, (j) 14\frac{1}{4}.$$

4. Add the following:

$$(a) \frac{1}{2} + \frac{2}{3} \quad (e) \frac{2}{3} + \frac{3}{5} \quad (h) 6\frac{1}{6} + 5\frac{2}{19}$$

$$(b) \frac{1}{2} + \frac{3}{4} \quad (f) \frac{1}{8} + \frac{3}{8} \quad (i) \frac{1}{2} + \frac{2}{3} + \frac{4}{6}$$

$$(c) \frac{1}{4} + \frac{5}{8} + \frac{3}{16} + \frac{1}{2} \quad (g) 2\frac{1}{2} + 1\frac{5}{8} \quad (j) \frac{1}{3} + \frac{2}{5} + \frac{5}{7}$$

$$(d) \frac{1}{4} + \frac{1}{5}$$

5. Subtract:

$$(a) \frac{5}{8} - \frac{1}{4} \quad (e) 5\frac{3}{4} - 2\frac{1}{2} \quad (h) \frac{1}{8} - \frac{1}{6}$$

$$(b) \frac{6}{7} - \frac{2}{3} \quad (f) 16\frac{2}{3} - 12\frac{1}{6} \quad (i) \frac{9}{11} - \frac{4}{6}$$

$$(c) \frac{7}{12} - \frac{3}{8} \quad (g) \frac{5}{9} - \frac{1}{3} \quad (j) 12\frac{5}{8} - 11\frac{7}{8}$$

$$(d) 12\frac{1}{25} - \frac{2}{5}$$

6. Multiply:

$$(a) \frac{1}{2} \times \frac{1}{6} \quad (e) \frac{2}{5} \times 10\frac{1}{13} \quad (h) \frac{6}{7} \times \frac{7}{6} \times \frac{2}{3}$$

$$(b) \frac{1}{3} \times \frac{2}{5} \quad (f) \frac{5}{6} \times \frac{3}{5} \quad (i) \frac{4}{9} \times \frac{3}{6}$$

$$(c) \frac{1}{4} \times \frac{4}{5} \quad (g) \frac{3}{7} \times 21\frac{1}{24} \quad (j) 5\frac{1}{11} \times 22\frac{2}{25} \times \frac{1}{2}$$

$$(d) \frac{1}{8} \times \frac{1}{6}$$

7. Divide:

$$(a) \frac{1}{2} \div \frac{1}{6} \quad (d) \frac{1}{3} \div \frac{1}{6} \quad (g) 7 \div \frac{3}{4} \quad (i) \frac{7}{8} \div \frac{3}{4}$$

$$(b) \frac{1}{4} \div \frac{1}{6} \quad (e) 2\frac{1}{2} \div \frac{4}{5} \quad (h) 5 \div \frac{3}{4} \quad (j) \frac{2}{7} \div 5$$

$$(c) \frac{2}{3} \div \frac{2}{3} \quad (f) 3\frac{1}{3} \div \frac{1}{3}$$

Decimal Fractions

A decimal fraction is one or more of the decimal parts of a unit. It results from the division of a unit into tenths, tenths into hundredths, hundredths into thousandths, etc., called the *decimal division*. The denominator of a decimal fraction is 10, 100, 1000, etc. Decimal fractions may be expressed in three ways:

(1) By words: as, three tenths, fifteen hundredths, one hundred twenty-five thousandths.

(2) By writing the denominator under the numerator: as $\frac{3}{10}$, $\frac{15}{100}$, $\frac{125}{1000}$.

(3) By omitting the denominator and, writing the numerator in decimal form: as .3, .15, .125.

The *decimal form* is so called because only decimal fractions can be thus expressed. When a decimal fraction is written in the decimal form, it is called a *decimal*.

The *decimal point* is a period placed at the left of the order of tenths, to designate the decimal orders. The orders on the left of the *decimal point* are *integral* and those on the right are *decimal*. The decimal orders are called *decimal places*.

The accompanying table gives the names of six integral and six decimal orders:

6 Hundred-thousands	5 Ten-thousands	4 Thousands	3 Hundreds	2 Tens	1 Units	. Decimal Point	1 st Tenths	2 Hundredths	3 Thousandths	4 Ten-Thousandths	5 Hundred-Thousandths	6 Millionths
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The successive decimal orders decrease in value from left to right, and increase from right to left in the same manner as integral orders. Hence, the removal of a decimal figure one order to the left multiplies its value by 10, and its removal one order to the right divides its value by 10. Annexing ciphers to a decimal, or decimal ciphers to an integer, does not change its value. Removing ciphers from the right of a decimal, or decimal ciphers from the right of an integer, does not change its value.

Addition and Subtraction of Decimals. To add and subtract decimals: (1) write the numbers so that figures of the same order shall be in the same column; (2) add and subtract as in the case of integers and place the decimal point at the left of the tenths order in the answer.

Multiplication of Decimals. To multiply one decimal by another, multiply as in the multiplication of integers, and point off as many decimal places in the product as there are in both multiplicand and multiplier. To multiply a decimal by 10, 100, 1000, etc., remove the decimal point as many places to the right as there are ciphers in the multiplier.

Division of Decimals. To divide one decimal by another, divide as in the division of integers, and point off as many decimal places in the quotient as the number of decimal places in the dividend exceeds the number in the divisor.

When the divisor contains more decimal places than the dividend, supply the deficiency in the dividend by *annexing* decimal ciphers.

When the quotient has not enough decimal figures, supply the deficiency by *prefixing* decimal ciphers.

When there is a remainder, the division may be continued by annexing ciphers, each cipher thus annexed adding one decimal place to the dividend. Sufficient accuracy is usually secured by carrying the division to three decimal places.

To divide a decimal by 10, 100, 1000, etc., remove the decimal point as many places to the left as there are ciphers in the divisor.

Exercises in Decimals

1. Express as decimals:

- | | | | |
|------------------------|---------------------------|------------------------|----------------------------|
| (a) $\frac{3}{10}$ | (f) $\frac{425}{10\ 000}$ | (k) $\frac{425}{1000}$ | (o) $\frac{9}{100}$ |
| (b) $\frac{6}{100}$ | (g) $\frac{5}{10}$ | (l) $\frac{7}{1000}$ | (p) $\frac{23}{1000}$ |
| (c) $\frac{25}{100}$ | (h) $\frac{9}{10}$ | (m) $\frac{5}{10}$ | (q) $\frac{305}{1000}$ |
| (d) $\frac{21}{100}$ | (i) $\frac{23}{10}$ | (n) $\frac{5}{1000}$ | (r) $\frac{425}{100\ 000}$ |
| (e) $\frac{225}{1000}$ | (j) $\frac{34}{100}$ | | |

2. Add:

- (a) .5, .3, .25, .465, .725
 (b) .4605, .907, 27.5008, 15.34
 (c) Thirty-six hundredths; seventy-five millionths; 15 ten-thousandths and 27 hundredths.
 (d) Forty-five thousandths; 25 millionths; 12 ten-thousandths; 5 hundredths.

3. Subtract:

- (a) .62481 from .75930
 (b) 143.763 from 150.6
 (c) 1.6425 from 3.950
 (d) 9.08 + 43.375 from 47.065 + 36.87
 (e) .14924 from .24365.

4. Multiply:

- (a) .125 by .015
 (b) 2.065 by 1.0625
 (c) 4.35 by 3.1416
 (d) .065 by 12.3
 (e) 22.5 by 1.105
 (f) .347 by .73
 (g) 650 by 2.4
 (h) 47.5 by .0025

5. Divide:

- (a) 12 by .625
 (b) 25 by 3.25
 (c) 39.6 by 2.78
 (d) 5.025 by 1.2
 (e) .624852 by 3.16
 (f) 106.4 by 13.3
 (g) 17.28 by .48
 (h) .9408 by 8.4

Converting Common Fractions Into Decimals and Vice Versa

To convert a common fraction into a decimal, divide the numerator of the fraction by the denominator; for example, $\frac{1}{2} = 1 \div 2 = .5$.

To convert a decimal into a common fraction drop the decimal point and write the denominator; i.e., $.5 = \frac{5}{10} = \frac{1}{2}$.

The *decimal point* is a period placed at the left of the order of tenths, to designate the decimal orders. The orders on the left of the decimal point are integral and those on the right are decimal. The decimal orders are called *decimal places*.

The accompanying table gives the names of six integral and six decimal orders:

6Hundred-thousands	5Ten-thousands	4Thousands	3Hundreds	2Tens	1Units	. Decimal Point	1Tenths	2Hundredths	3Thousandths	4Ten-Thousandths	5Hundred-Thousandths	6Millionths
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The successive decimal orders decrease in value from left to right, and increase from right to left in the same manner as integral orders. Hence, the removal of a decimal figure one order to the left multiplies its value by 10, and its removal one order to the right divides its value by 10. Annexing ciphers to a decimal, or decimal ciphers to an integer, does not change its value. Removing ciphers from the right of a decimal, or decimal ciphers from the right of an integer, does not change its value.

Addition and Subtraction of Decimals. To add and subtract decimals: (1) write the numbers so that figures of the same order shall be in the same column; (2) add and subtract as in the case of integers and place the decimal point at the left of the tenths order in the answer.

Multiplication of Decimals. To multiply one decimal by another, multiply as in the multiplication of integers, and point off as many decimal places in the product as there are in both multiplicand and multiplier. To multiply a decimal by 10, 100, 1000, etc., remove the decimal point as many places to the right as there are ciphers in the multiplier.

Division of Decimals. To divide one decimal by another, divide as in the division of integers, and point off as many decimal places in the quotient as the number of decimal places in the dividend exceeds the number in the divisor.

When the divisor contains more decimal places than the dividend, supply the deficiency in the dividend by *annexing* decimal ciphers.

Exercises in Percentage

1. Change to decimal fractions:

(a) $\frac{3}{10}$, (b) $\frac{25}{100}$, (c) $\frac{31}{100}$, (d) $\frac{9}{1000}$, (e) $\frac{23}{1000}$, (f) $\frac{7}{10000}$, (g) 5 per cent, (h) .25 per cent, (i) $\frac{1}{2}$ per cent, (j) $16\frac{2}{3}\%$, (k) $12\frac{1}{2}\%$, (l) 20%, (m) 25 per cent.

2. Change to common fractions and reduce to lowest terms:

(a) 2%, (b) 5%, (c) 6%, (d) $8\frac{1}{5}\%$, (e) 10%, (f) $12\frac{1}{2}\%$, (g) $14\frac{3}{4}\%$, (h) 20%, (i) 25%, (j) $33\frac{1}{3}\%$.

3. Change the following fractions to percentage:

(a) $\frac{1}{8}$, (b) $\frac{1}{4}$, (c) $\frac{1}{2}$, (d) $\frac{1}{3}$, (e) $\frac{1}{5}$, (f) $\frac{1}{6}$, (g) $\frac{3}{5}$, (h) $\frac{3}{4}$, (i) $\frac{4}{5}$, (j) $\frac{5}{6}$, (k) .2, (l) .3, (m) .5, (n) .05, (o) .07, (p) .025, (q) .065, (r) .25 (s) .01, (t) .002.

4. Find:

(a) 10 per cent of 500
(b) $16\frac{2}{3}$ per cent of 300
(c) $8\frac{1}{2}$ per cent of 360

(d) 75 per cent of 400
(e) $\frac{1}{10}$ per cent of 1000
(f) $12\frac{1}{2}$ per cent of 320

5. What per cent of:

(a) 10 is 2
(b) 45 is 9
(c) 50 is 35

(d) 100 is $33\frac{1}{3}$
(e) 20 is $6\frac{2}{3}$
(f) 6 is 1.5

(g) 25 is 1
(h) 200 is 25

(i) 80 is 16
(j) 40 is 8

Ratio and Proportion

Ratio means the relation which one quantity bears to another. The ratio 1:20 means that for every twenty parts of one substance there is one part of another substance; for example, in a 1:20 solution of lysol, there is one part of lysol in every 20 parts of solution. In any quantity of the solution, the amount of solute would be in the same relation to the whole as 1 bears to 20, or in other words, the ratio shows the relation between the solute and the whole solution.

The ratio of one amount to an amount expressed in terms of the same unit is the number of units in the first divided by the number of units in the second. The ratio of two ounces of lysol to ten ounces of water is 2 to 10 or 1 to 5 or $\frac{1}{5}$. The ratio may be written $\frac{1}{5}$ or 1:5. The two numbers compared are called the terms of the ratio. The first term of a true ratio is always one (1).

To change ratio to per cent, make the first term of the ratio the numerator of a fraction whose denominator is the second term of the ratio. Divide the numerator by the denominator and multiply by 100.

$$1:5 = \frac{1}{5} \times 100\% = 20\%$$

$$5:1 = \frac{5}{1} \times 100\% = 500\%$$

Exercises

1. Convert into decimals:

(a) $\frac{1}{8}$	(e) $\frac{1}{2}$	(i) $\frac{5}{8}$	(m) $\frac{7}{8}$	(q) $\frac{4}{25}$
(b) $\frac{3}{20}$	(f) $\frac{1}{10}$	(j) $\frac{3}{40}$	(n) $\frac{1}{5}$	(r) $\frac{2}{5}$
(c) $\frac{1}{4}$	(g) $\frac{3}{4}$	(k) $\frac{2}{3}$	(o) $\frac{3}{200}$	(s) $\frac{3}{5}$
(d) $\frac{3}{8}$	(h) $\frac{2}{25}$	(l) $\frac{1}{50}$	(p) $\frac{5}{80}$	

2. Express as common fractions in their lowest terms:

(a) .75	(e) .0625	(i) .125	(m) .075	(q) .275
(b) .0095	(f) .0125	(j) .765	(n) .025	(r) .36
(c) .625	(g) .08	(k) .035	(o) .512	(s) .024
(d) .325	(h) .0032	(l) .0285	(p) .725	(t) .15

Percentage

Per cent means hundredths. One per cent of a number is one hundredth of it ($\frac{1}{100}$), two per cent, two hundredths ($\frac{2}{100}$), etc. The term "per cent" is usually denoted by the symbol %. For example 5% means five per cent or $\frac{5}{100}$ or decimally .05.

With reference to solutions, per cent means the number of parts of solute contained in 100 parts of solution. Thus a five per cent solution of lysol means that $\frac{5}{100}$ of that total amount of the solution is lysol.

To change per cent to a decimal fraction, omit the per cent sign and express as hundredths decimally. Thus, 5% becomes .05; 20% becomes .20 or .2.

To change per cent to a common fraction, omit the symbol and write the per cent as the numerator and 100 as the denominator of the fraction, thus 5% becomes $\frac{5}{100}$; 25%, $\frac{25}{100}$ or $\frac{1}{4}$.

To change a decimal fraction to per cent, multiply by 100 and write as a whole number with the per cent sign. Thus $.2 \times 100 = 20$ per cent; $.02 \times 100 = 2$ per cent.

To change a common fraction to per cent, divide the numerator by the denominator and multiply the resulting decimal by 100. Thus $\frac{2}{50} = .02 \times 100 = 2\%$.

To find a certain per cent of any number, multiply the number by the per cent expressed as a common or decimal fraction. Thus, 1 per cent of 500 = $500 \times \frac{1}{100} = 5$. To determine what per cent any quantity is of a larger quantity, divide the smaller quantity by the larger and multiply the quotient by 100.

17. State the rule for changing a decimal fraction to per cent; a common fraction to per cent.
18. How may a certain per cent of any number be found? How may it be determined what per cent any quantity is of a larger quantity?
19. What does the term "ratio" mean?
20. How may a common fraction be changed to a ratio? A decimal fraction to a ratio? A per cent to a ratio?
21. Change the following ratios to percentages:

1-25	1-12½	1-20	1-3	1-5	1-2	1-8	1-4
1-6	1-40	1-50	1-100	1-7	1-500	1-1000	1-10,000

22. Change the following percentages to ratios:

2 %	4%	5%	6%	10%	12½%	25%	16⅔%
33⅓%	½%	⅓%	⅓%	⅒%	⅒%	⅒%	20 %

Review problems for students who have some knowledge of the metric and apothecary systems:

1. What is the percentage strength of a solution of which a liter contains 25 grams of solute?
2. What is the ratio strength of a pint of solution which contains 50 grains of drug?
3. What is the percentage strength of 500 c.c. of solution that contains 50 cc. of alcohol?
4. If a solution contains 0.5 Gm. of drug to 50 cc., what is the percentage strength?
5. What is the percentage strength of a pint of solution which contains 30 grains of drug?
6. Determine the ratio strength of a liter of bichloride of mercury which contains two 7½ grain tablets.
7. Determine the ratio strength of an ounce of solution which contains 15 grains of drug.
8. If a dram of solution contains 5 grains of a drug, what is the percentage strength?
9. If a quart of a solution contains 240 grains of a drug, what is the ratio strength?
10. If 15 minims of solution contain one grain of phenol, what is the ratio strength?
11. What is the percentage strength of five ounces of solution which contains 3 drams of silver nitrate?
12. 60 c.c. of a solution contain 30 grains of drug. What is the ratio strength?
13. Determine the percentage strength of a dram of solution which contains 0.05 Gm. of drug.
14. 100 cc. of a solution contain 30 grains of solute. What is the percentage strength?
15. What is the ratio strength of a solution of which 1 dram contains 0.065 Gm. of drug?

To change per cent to ratio, change the per cent to a fraction which is reduced to its lowest terms. The numerator of the fraction is the first term of the ratio, and the denominator is the second term of the ratio.

$$50\% = \frac{5}{100} = \frac{1}{2} = 1:2$$

$$2\% = \frac{2}{100} = \frac{1}{50} = 1:50$$

$$\frac{1}{2}\% = \frac{1/2}{100} = \frac{1}{200} = 1:200$$

A proportion is an expression of the equality between two ratios. For example, 1:2 as 5:10 or $\frac{1}{2} = \frac{5}{10}$. The first and last terms are called the extremes; the second and third terms are called the means. In any proportion the product of the means equals the product of the extremes. In the above proportion $1 \times 10 = 10$ and $2 \times 5 = 10$.

When one of the extremes in a proportion is not known, it can be found by dividing the product of the means by the extreme that is known. If one of the means is not known, it can be found by dividing the product of the extremes by the mean that is known.

Questions for Review

1. Give the rules for combining Roman numerals to express numbers.
2. What is a fraction? How is it expressed? What is meant by the "terms" of a fraction?
3. Define
 - (a) proper fraction
 - (b) improper fraction
 - (c) complex fraction
 - (d) mixed number
4. How may a fraction be reduced to its lowest terms? To higher terms?
5. What is meant by the least common denominator (L. C. D.)?
6. How may fractions be reduced to equivalent fractions with a least common denominator?
7. State the rule for
 - (a) the addition of common fractions
 - (b) the subtraction of fractions
8. Give the rule for the multiplication of fractions.
9. What is the rule for the division of fractions?
10. What is a decimal fraction?
11. What is meant by the term "decimal place"? Name the first six decimal places.
12. Give the rule for
 - (a) the addition of decimals
 - (b) the subtraction
 - (c) multiplication
 - (d) division
13. How may a common fraction be converted into a decimal? A decimal into a common fraction?
14. What does the term "per cent" mean?
15. What fractional part of anything is 5 per cent?
16. How may per cent be changed to a decimal fraction? To a common fraction?

When the symbols are used the quantity is expressed in Roman numerals which are placed after the symbols: for example, three grains are written, gr. iii; five drams, \mathfrak{z} v; ten ounces \mathfrak{z} x. Fractions are expressed in Arabic numerals; gr. $\frac{1}{4}$, gr. $\frac{1}{8}$, gr. $\frac{1}{2}$; the symbol "ss" may be used for $\frac{1}{2}$; thus, two and one-half grains, gr. iiss.

The minim is often assumed to be identical with the drop (gtt. from *L. gutta*) but such measurement is inaccurate. A minim of water or of an aqueous solution is approximately equal to a drop; a minim of an alcoholic solution such as tincture of digitalis equals approximately two drops; a minim of ether contains three drops and a

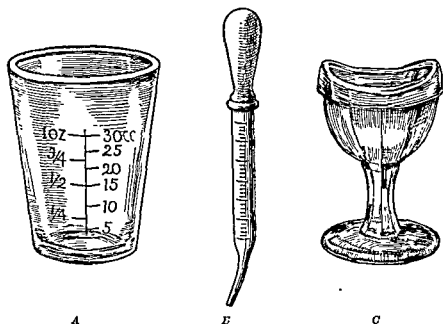


FIG. 3.—A, A medicine glass graduated in both ounces and cubic centimeters; B, a graduated medicine dropper; and C, an eyecup. The cup is filled with the solution (Collyrium), the patient looks down, and the cup is brought up in front of the eye and held against the circumference of the eyesocket. By winking the eye or tilting the head back and forth the eye can be washed. (From Jackson: *Experimental Pharmacology and Materia Medica*.)

minim of chloroform equals approximately four drops. A minim of a gummy substance is less than a drop. Minims should always be measured when minims are ordered, and a minim glass or minim pipette used to measure accurately. When drops are ordered, they may be measured by means of a medicine dropper.

Exercises

1. Read the following:

- | | | | | |
|-------------------------|--------------------------|-------------------------|-----------------------|-------------------------|
| (a) \mathfrak{z} iiss | (c) \mathfrak{z} ss | (e) \mathfrak{m} viii | (g) \mathfrak{z} iv | (i) \mathfrak{m} xxiv |
| (b) gr. xiii | (d) \mathfrak{z} xviii | (f) gr. xxx | (h) \mathfrak{z} vi | (j) O v |

CHAPTER V

WEIGHTS AND MEASURES

There are two systems of weighing and measuring drugs in use in the United States at the present time, the *Apothecaries' System* and the *Metric System*.

APOTHECARIES' SYSTEM

The Apothecaries' System of weights and measures is part of the system used in England at the time of the colonization of our country. It has long since been superseded there by the Imperial System which is official in Great Britain.

Weight

The smallest weight in use, or the *unit of weight*, is the grain, which originally meant a grain of wheat. The other units are the scruple, the dram, the ounce, and the pound. The scruple is seldom used; quantities less than one dram are usually expressed in grains. The symbol lb. is the abbreviation for *libra*, the Latin word meaning pound.

TABLE OF WEIGHT

20 grains	= 1 scruple	(℥)
3 scruples or 60 grains	= 1 dram	(ʒ)
8 drams or 480 grains	= 1 ounce	(ʒ)
12 ounces	= 1 pound	(lb.)

The unit of fluid measure is a minim, approximately the quantity of water that would weigh a grain. The symbol O is the abbreviation of the Latin word *octarius*, meaning an eight; C, for the Latin word *congius*, meaning a vessel holding a gallon.

TABLE OF FLUID MEASURE

60 minims (℥)	= 1 fluidram	(fʒ)
8 fluidrams or 480 minims	= 1 fluidounce	(+ʒ)
16 fluidounces	= 1 pint (pt. or O)	
2 pints	= 1 quart	(qt)
4 quarts	= 1 gallon	(C)

5. Dissolve gr. xxx of salt in f $\bar{3}$ liiss of water. How many grains of salt would there be in 40 η of the solution?
6. Using the colored solution to represent alcohol, add one fluidram of alcohol to 4 fluidrams of water. What part of the solution will be alcohol? How many minims of alcohol would there be in 60 η of the solution?
7. Add f $\bar{3}$ ii of alcohol to f $\bar{3}$ iv of water. What part of the solution is alcohol? How many minims of alcohol in each fluidram of solution?

METRIC SYSTEM

The metric system is the system prescribed by law in most European countries, and several legislative attempts have been made to render its use obligatory in the United States. Its official recognition is merely a question of time, however, as its use is constantly extending. It is now used in the sciences and pharmacy, in weighing foreign mail, in weighing at the mints and in certain other government departments, particularly the medical department of the army and navy.

History

The metric system of weights and measures was invented by the French in the latter part of the eighteenth century. For this purpose a committee of the Academy of Sciences, consisting of five men, was appointed under authority of the government. They had two preconceived ideas regarding the proposed system: first, that the standards should be based upon some unalterable object in nature, so that the correctness of the measures accepted as models might be redetermined, if necessary; second, that the system should employ the decimal scale. Of the three natural linear bases proposed, namely, the length of a second's pendulum, a fourth of the earth's circumference measured along the equator, and a fourth of the earth's circumference measured across the poles, the committee recommended the last, one ten-millionth of which should be the standard unit of linear measure. They calculated the distance from the equator to the north pole from surveys made along the meridian which passes through Paris, and this distance, divided by 10,000,000 was chosen as the unit of length, the meter. The meter is the fundamental unit of the metric system. A bar of platinum was constructed of this length and deposited in the French Archives to serve as a model for the meter measures intended for actual use. There was also constructed and deposited in the Archives, a weight of platinum of such size as to counterpoise in vacuo one cubic decimeter of water at its greatest density. This weight constituted the fundamental standard of mass and was to serve as the model for the Kilogram weights (and indirectly for the other weights) intended for actual use.

2. Write the following expressions as they should be written in a prescription:

15 minims, 3 fluidrams, 7 fluidounces, 1 pint, $2\frac{1}{2}$ drams, 20 grains, 12 minims, 5 ounces, $\frac{1}{2}$ ounce.

3. How many grains are there in:

- | | | | | |
|------------------------|-------------------------|---------------------|-----------------------|----------------------|
| (a) 3 iii | (c) 3 i | (e) 1b. i | (g) $\frac{3}{4}$ ss | (i) $\frac{3}{4}$ iv |
| (b) $\frac{3}{4}$ viii | (d) $\frac{3}{4}$ viiss | (f) $\frac{3}{4}$ v | (h) $\frac{3}{4}$ lss | (j) $\frac{3}{4}$ ix |

4. How many minims are there in:

- | | | | | |
|-----------------------|-----------------------------------|-----------------------|-----------------------|--------------------------|
| (a) $\frac{f3}{3}$ i | (c) $\frac{f3}{3}$ ss | (e) 1 qt. | (g) O iii | (i) $\frac{f3}{3}$ liiss |
| (b) $\frac{f3}{3}$ iv | (d) $\frac{f3}{3}$ $1\frac{1}{2}$ | (f) $\frac{f3}{3}$ in | (h) $\frac{f3}{3}$ iv | (j) O ss |

5. What part of a dram is gr. xv, gr. xx, gr. xxx, gr. xlv, gr. i?

What part of an ounce is $\frac{3}{4}$ iv, $\frac{3}{4}$ ii, $\frac{3}{4}$ iii, $\frac{3}{4}$ ss, $\frac{3}{4}$ vii?

What part of a fluidram is $\frac{m}{4}$ xv, $\frac{m}{4}$ xx, $\frac{m}{4}$ xxx, $\frac{m}{4}$ xlv, $\frac{m}{4}$ l?

What part of a fluidounce is $\frac{f3}{3}$ ii, $\frac{f3}{3}$ ss, $\frac{f3}{3}$ iv, $\frac{f3}{3}$ vi, $\frac{f3}{3}$ v?

6. Add the following and express in fluidrams: O $\frac{ss}{4}$, $\frac{m}{4}$ xx, $\frac{f3}{3}$ vi, $\frac{m}{4}$ 480.

7. A physician's prescription calls for gr. xxiv of a drug. This would be what part of an ounce?

8. One headache powder contains gr. v of the drug; how many drams of this drug would be required to make up 60 powders?

9. How much morphine sulfate would be required to make up two fluidounces of solution if every 20 minims of the solution is to contain gr. $\frac{1}{4}$?

10. If a pint of solution contains $\frac{3}{4}$ ii of drug, how many grains in each fluidounce of solution?

Laboratory Suggestions

MATERIALS FOR USE—Apothecaries' scales and measures; colored solution and salt.

1. With a minim measure determine the number of minims in:

- (a) a fluidram ----- (b) two fluidounces ----- (c) a fluidounce -----

Why would a minim glass be unsuitable to measure out several fluidounces of a solution?

2. With a fluidram measure determine how many fluidrams there are in a fluidounce -----; in a pint ----- What kind of an apothecary measure would you select to measure out $\frac{1}{2}$ pint of a solution if you had the following to choose from: minim glass; fluidram measure; fluidounce measure? Why?

3. Weigh out 60 grains of salt on an apothecary scale. This corresponds with how many drams?

4. Dissolve $\frac{3}{4}$ i of salt in $\frac{f3}{3}$ iv of water. How many grains of salt are there in each fluidounce of solution? In each fluidram?

Tables

TABLE OF LINEAR MEASURE

10 millimeters (mm.)	=	1 centimeter (cm.)
10 centimeters	=	1 decimeter (dm.)
10 decimeters	=	1 meter (M.)
10 meters	=	1 dekameter (Dm.)
10 dekameters	=	1 hectometer (Hm.)
10 hectometers	=	1 kilometer (Km.)

TABLE OF CAPACITY

10 milliliters (mil)	=	1 centiliter (cl.)
10 centiliters	=	1 deciliter (dl.)
10 deciliters	=	1 liter (L.)
10 liters	=	1 dekaliter (Dl.)
10 dekaliters	=	1 hectoliter (Hl.)
10 hectoliters	=	1 kiloliter (Kl.)

Since the milliliter (mil) and the cubic centimeter (cc.) both represent the one thousandth part of a liter, the terms may be used interchangeably. The Pharmacopoeia once adopted the former term but has returned to the use of cc.

The unit of weight is the gram. It is the weight of one cubic centimeter of distilled water at 4° Centigrade. The official abbreviation of gram given in the Pharmacopoeia is Gm.

TABLE OF WEIGHT

10 milligrams (mg.)	=	1 centigram (cg.)
10 centigrams	=	1 decigram (dg.)
10 decigrams	=	1 gram (Gm.)
10 grams	=	1 dekagram (Dg.)
10 dekagrams	=	1 hectogram (Hg.)
10 hectograms	=	1 kilogram (Kg.)

In reading a whole number expressing a metric quantity only one unit is used, however large the number, i.e., 2750 Gm. is read, twenty-seven hundred and fifty grams, not two kilograms, seven hectograms, five dekagrams; 7500 c.c. is read, seven thousand five hundred or seventy-five hundred cubic centimeters.

In expressing a fraction of a gram, the terms decigram and centigram are seldom used. The quantity is expressed in its equivalent grams or milligrams; for example, 6 decigrams, written 0.6 Gm., is called six-tenths gram; 5 centigrams, written 0.05 Gm., is called preferably fifty milligrams. The thousandth part of a gram and multiples or fractions of it are commonly expressed as milligrams; i.e., 0.001 Gm. may be expressed as 1 mg.; 0.003 Gm. as 3 mg., etc., and 0.0005 Gm. as 0.5 mg., etc.

To insure accuracy in reading, a zero should always be used before the decimal point in writing a fractional part of a metric unit;

The metric standards were adopted in France in 1799. In 1875 the International Metric Convention met in Paris. Seventeen countries including the United States participated. This convention resulted in the foundation of the International Bureau of Weights and Measures, whose first work was the preparation of an international standard meter bar and an international standard kilogram weight, and duplicates for each of the countries which have contributed to the support of the bureau. For the international standard meter, a bar of platinum iridium was selected and two lines drawn on its surface at a distance from each other equal to one meter measured when the bar is at the temperature of melting ice (0° C.). The distance between these lines is the official unit of the metric system. The international standards were placed in the custody of the International Bureau of Weights and Measures near Paris. The duplicates were distributed by lot, the United States drawing meters No. 21 and No. 27 and kilograms No. 4 and No. 20. Meter No. 27 and kilogram No. 20 were selected as our national standard and are carefully preserved in the United States Bureau of Standards at Washington, D. C. Meter No. 21 and kilogram No. 4 are used as working standards.

Terminology

The primary metric units with which pharmacy is concerned are the following:

Meter—length
 Liter—capacity
 Gram—weight

Secondary units, differing from each other by ten or some multiple of ten, are formed by joining certain Greek and Latin prefixes to the names of the primary units.

The prefixes used to designate subdivision of the unit, deci (0.1) centi (0.01) milli (0.001) are from the Latin and those used to designate multiples, deka (10) hecto (100) and kilo (1000) are from the Greek.

Milli	0.001
Centi	0.01
Deci	0.1
Unit-meter, liter, gram	1.0
Deka	10
Hecto	100.
Kilo	1000.

Tables

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10 liters	=	1 dekaliter (Dl.)
10 dekaliters	=	1 hectoliter (Hl.)
10 hectoliters	=	1 kiloliter (Kl.)

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10 grams	=	1 dekagram (Dg.)
10 dekagrams	=	1 hectogram (Hg.)
10 hectograms	=	1 kilogram (Kg.)

In reading a whole number expressing a metric quantity only one unit is used, however large the number, i.e., 2750 Gm. is read, twenty-seven hundred and fifty grams, not two kilograms, seven hectograms, five dekagrams; 7500 c.c. is read, seven thousand five hundred or seventy-five hundred cubic centimeters.

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To insure accuracy in reading, a zero should always be used before the decimal point in writing a fractional part of a metric unit:

i.e., 0.5 Gm., 0.6 cc., 0.001 L. The abbreviations for gram, mil or cubic centimeter may be omitted. In that case, 1.0 means one gram when expressing weight or one cc. when expressing quantity.

The metric system has many advantages over the apothecaries' system, chief of which are: all the standard units of weight and measure bear a simple relation to the fundamental unit, the meter; the prefixes deci, centi, milli, deka, hecto, and kilo have a numerical significance, and have other applications in our language, which make them readily understood; the uniform decimal scale of relation between the successive units makes the use of the decimal notation possible; and finally, the system is a universal one.

Exercises

1. Read aloud: (a) 2500 Gm, (b) 0.065 Gm, (c) 2.5 Gm, (d) 0.6 L., (e) 0.005 L., (f) 3.25 Gm., (g) 0.03 Gm., (h) 0.025 Gm., (i) 0.2 Gm.

2. State aloud the English meaning of the following:

milli	kilo	deci	hecto	centi	kilo
centi	milli	kilo	deci	milli	hecto

Continue this drill until the numerical equivalents can be stated instantaneously.

3. State aloud the metric prefixes of the following numbers, applying them to (1) meter (2) gram (3) liter:

(a) 0.1 (b) 0.01 (c) 100.0 (d) 0.001 (e) 1000.0 (f) 10.0

4. (a) What part of a meter is a decimeter?
 (b) What part of a decimeter is a centimeter?
 (c) What part of a centimeter is a millimeter?
 (d) What part of a meter is a millimeter?

5. (a) ---
 (b) ---
 (c) ---
 (d) ---

6. Change to grams: (a) 2500 mg., (b) 360 dg., (c) 25 cg., (d) 27 mg., (e) 420 dg.

7. Convert into milligrams: (a) 5 Gm, (b) 3 Dg., (c) 54 cg., (d) 32 Dg., (e) 0.064 Gm.

8. Add and express in grams:

- (a) 6 Gm., 8 dg., 3 cg., 64 mg.
 (b) 2 Gm., 5 cg., 4 dg., 15 mg.
 (c) 7 mg., 2.5 Gm., 6 cg., 5 mg.
 (d) 125 mg., 8 cg., 3 dg., 4.0 Gm.

9. A preparation of medicine is made by dissolving 15 mg. of the drug in 240 c.c. of water. If 3 mg. is the dose, how many cubic centimeters must be given for each dose?

10. If the dose of cascara sagrada is 4 cc., how many doses will there be in $\frac{1}{2}$ liter?

11. If 4 Gm. of drug are added to 400 cc. of water, how many milligrams of drug is there in each milliliter of solution?

12. If 20 cc. of alcohol are added to 80 cc. of water to make a certain desired strength of solution, how much alcohol would be required to make a liter of this solution?

Laboratory Suggestions

MATERIALS FOR USE.—Glass measures marked in cubic centimeters, gram scales, salt, water, colored solution for alcohol.

1. Study the gram scale. Balance it; note how the scale is marked to indicate the subdivisions of the gram.

2. Weight out 2 grams of salt and add it to 20 cc. of water; notice how much constitutes each of these amounts. Is the volume of the liquid noticeably changed? Why? How much salt is there in each cubic centimeter of solution?

3. Normal salt solution is made by adding 9 Gm. of salt to 1000 cc. of water; weigh out the amount of salt needed for $\frac{1}{2}$ liter of normal salt solution.

4. Add 5 cc. of alcohol to 25 cc. of water. Is the volume of the liquid increased? Why? What part of the finished solution is alcohol? How much alcohol would be needed to make $1\frac{1}{2}$ liters of solution of the same strength?

5. Add 20 ml. of alcohol to 60 cc. of water. How much alcohol is there in each cubic centimeter of solution?

Approximate Equivalents

Since both the apothecaries' and the metric systems are used in most hospitals today, the student should know both systems well and be able to change rapidly and accurately from one system to the other. The accompanying table of approximate equivalents indicates the relation between the units of the two systems:

TABLE OF APPROXIMATE EQUIVALENTS

1 grain	=	0.065 Gm.
1 minim	=	0.065 cc.
15 grains	=	1 Gm.
15 minims	=	1 cc.
1 dram	=	4 Gm.
1 fluidram	=	4 cc.
1 ounce	=	30 Gm.
1 fluidounce	=	30 cc.
1 pint	=	500 cc.
1 quart	=	1000 cc.

Converting One System Into the Other

By application of the above table, the following rules may be deduced for changing from one system to the other:

Metric to Apothecaries'

Rules: (1) To convert grams to grains, either (a) multiply by 15, since there are approximately 15 grains in 1 gram, or (b) divide by 0.065, since 1 grain equals 0.065 Gm.

Example: Convert 15.0 Gm. to grains:

$$\begin{aligned}
 1.0 \text{ Gm.} &= 15 \text{ gr.} \\
 15.0 \text{ Gm.} &= 15 \times 15 = 225 \text{ gr.} \\
 1 \text{ gr.} &= 0.065 \text{ Gm.} \\
 15 \text{ Gm.} &= 15 \div 0.065 = 230.7
 \end{aligned}$$

i.e., 0.5 Gm., 0.6 cc., 0.001 L. The abbreviations for gram, mil or cubic centimeter may be omitted. In that case, 1.0 means one gram when expressing weight or one cc. when expressing quantity.

The metric system has many advantages over the apothecaries' system, chief of which are: all the standard units of weight and measure bear a simple relation to the fundamental unit, the meter; the prefixes deci, centi, milli, deka, hecto, and kilo have a numerical significance, and have other applications in our language, which make them readily understood; the uniform decimal scale of relation between the successive units makes the use of the decimal notation possible; and finally, the system is a universal one.

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- (d) What part of a meter is a millimeter?

5. (a) How many grams in a dekagram?
- (b) How many dekagrams in a hectogram?
- (c) How many hectograms in a kilogram?
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By application of the above table, the following rules may be deduced for changing from one system to the other:

Metric to Apothecaries'

Rules: (1) To convert grams to grains, either (a) multiply by 15, since there are approximately 15 grains in 1 gram, or (b) divide by 0.065, since 1 grain equals 0.065 Gm.

Example: Convert 15.0 Gm. to grains:

$$\begin{aligned}
 1.0 \text{ Gm.} &= 15 \text{ gr.} \\
 15.0 \text{ Gm.} &= 15 \times 15 = 225 \text{ gr.} \\
 1 \text{ gr.} &= 0.065 \text{ Gm.} \\
 15 \text{ Gm.} &= 15 \div 0.065 = 230.7
 \end{aligned}$$

(The disparity in results from the two methods is due to the fact that we are dealing with approximate and not exact equivalents.)

(2) To convert cubic centimeters into minims, either (a) multiply by 15 since there are 15 minims in one cc., or (b) divide by 0.065 since one minim equals 0.065 cc. or mil.

(3) To convert grams or cubic centimeters into drams, divide by 4, since there are 4 grams or cubic centimeters in one dram.

(4) To convert grams or cubic centimeters into ounces, divide by 30, since there are approximately 30 grams or cubic centimeters in one ounce.

Apothecaries' to Metric

Rules: (1) To convert grains or minims into grams or cc., divide by 15 or multiply by 0.065.

(2) To convert drams into grams or cc. multiply by 4.

(3) To convert ounces into grams or cc., multiply by 30.

Approximate Equivalents in Everyday Use

The following equivalents have been adopted by the latest Pharmacopoeia:

gr. xv	=	1.0	Gm.		gr. $\frac{1}{20}$	=	0.0032	Gm.	=	3	mg.		
gr. x	=	0.6	Gm.		gr. $\frac{1}{30}$	=	0.0022	Gm.	=	2	mg.		
gr. v	=	0.3	Gm.		gr. $\frac{1}{40}$	=	0.0016	Gm.	=	1.5	mg.		
gr. iii	=	0.2	Gm.		gr. $\frac{1}{50}$	=	0.0013	Gm.	=	1.2	mg.		
gr. $1\frac{1}{2}$	=	0.1	Gm.	=	100	mg.	gr. $\frac{1}{60}$	=	0.001	Gm.	=	1	mg.
gr. l	=	0.06	Gm.	=	60	mg.	gr. $\frac{1}{100}$	=	0.0006	Gm.	=	.6	mg.
gr. $\frac{1}{2}$	=	0.03	Gm.	=	30	mg.	gr. $\frac{1}{120}$	=	0.0005	Gm.	=	.5	mg.
gr. $\frac{1}{4}$	=	0.015	Gm.	=	15	mg.	gr. $\frac{1}{150}$	=	0.0004	Gm.	=	.4	mg.
gr. $\frac{1}{8}$	=	0.008	Gm.	=	8	mg.	gr. $\frac{1}{200}$	=	0.0003	Gm.	=	.3	mg.
gr. $\frac{1}{15}$	=	0.004	Gm.	=	4	mg.	gr. $\frac{1}{300}$	=	0.0002	Gm.	=	.2	mg.

Exercises

1. Convert the following into their apothecaries' equivalents:

(a) 32.0	Gm.	(f) 3.065	Gm.	(k) 12.5	cc.
(b) 64.0	Gm.	(g) 0.6	Gm.	(l) 7.55	cc.
(c) 12.03	Gm.	(h) 0.0016	Gm.	(m) 0.6	cc.
(d) 14.0755	Gm.	(i) 0.425	Gm.	(n) 75.15	cc.
(e) 50.0	Mg	(j) 0.008	Gm.	(o) 625.1	cc.

2. Change to metric:

(a) 3 $1\frac{1}{2}$	(f) 3 v	(k) 5 vi
(b) 3 iii	(g) gr. $\frac{1}{100}$	(l) ℥ iiss
(c) 3 vii	(h) gr. $\frac{1}{250}$	(m) ℥ xlv
(d) 3 xx $\frac{1}{2}$	(i) gr. $\frac{1}{400}$	(n) ℥ xxx
gr. xi	(j) gr. $\frac{1}{40}$	(o) ℥ iv

3. Without consulting the text, practice giving metric equivalents for:

(a) gr. xv	(f) ℥ viiss	(k) gr. $\frac{1}{60}$	(p) gr. vii½
(b) gr. x	(g) ℥ x	(l) 5 1	(q) gr. $\frac{1}{8}$
(c) ℥ v	(h) gr. $\frac{1}{6}$	(m) gr. $\frac{1}{2}$	(r) gr. $\frac{1}{150}$
(d) gr. v	(i) 1 qt.	(n) gr. $\frac{1}{4}$	
(e) gr. 1½	(j) ℥ xv	(o) 1 pt.	

4. In the same way, give apothecaries' equivalents for:

(a) 1.0 Gm.	(f) 0.03 Gm.	(k) 500.0 cc.	(p) 0.065 Gm.
(b) 0.3 Gm.	(g) 4.0 cc.	(l) 0.0006 Gm.	(q) 0.008 Gm.
(c) 0.004 Gm.	(h) 1000 cc.	(m) 30.0 cc.	(r) 250.0 Gm.
(d) 1.0 cc.	(i) 0.5 Gm.	(n) 0.015 Gm.	
(e) 1½ cc.	(j) 0.1 Gm.	(o) 2.0 Gm.	

5. Change:

(a) 3 ounces to minims	(g) 1 liter to ounces
(b) 1 liter to pints	(h) 36 drams to grams
(c) 6.0 cc. to fluidrams	(i) 5.0 cc. to minims
(d) 75 grains to grams	(j) 3 pints to cc.
(e) 7.0 Gm. to grains	(k) 75.0 cc. to ounces
(f) 2 gallons to cc.	

6. If the dose of milk of magnesia is 15 cc., how many fluidounces would be necessary to give 10 doses?

7. If there are 7½ grains of drug in each 5 cc. ampoule of the preparation, how many grams of the drug in 4 ampoules?

8. If the dose of a certain medication is 0.1 Gm. and the tablets are marked 7½ grains, how many tablets will be given for each dose? How many tablets will be required for 10 doses?

9. If the dose of a medication is 4 cc., how many fluidounces would you order from the pharmacy in order to have 60 doses?

10. If a physician orders 15 mg. of a drug and the preparation comes marked "Tab. gr. $\frac{1}{8}$," how many tablets or what part of a tablet will you give?

Household Equivalents

Very often, in nursing in the home, a graduate for accurate measurement of liquids is not available and some household article may be used to measure, approximately, the amount required. The use of a drop (gtt.) for a minim is particularly inaccurate:

One level teaspoonful	= 1 dram or 60	= 4 grams (4.0 Gm.)
	gr. or 60 gtt.	
One level dessertspoonful	= 2 drams	= 8 grams (8.0 Gm.)
One level tablespoonful	= 4 drams	= 16 grams (16.0 Gm.)
One teacupful	= 6 fluidounces	= 180 cc. or mls
One tumblerful	= 8 fluidounces	= 240 cc. or mls

Problems

1. Using the above table—change 3 Gm. to grains.

$$\begin{aligned} 4 \text{ Gm.} &= 60 \text{ gr.} \\ 1 \text{ Gm.} &= 15 \text{ gr.} \\ 3 \text{ Gm.} &= 45 \text{ gr.} \end{aligned}$$

2. Using household measures, how would you measure:

(a) gr xxx	(e) 4.0 Gm.	(i) 30 0 cc.	(m) 3 ½
(b) 0.6 cc.	(f) 0 065 cc.	(j) 0 3 cc.	(n) 360 0 cc.
(c) 30 0 Gm.	(g) 4.0 cc.	(k) 6.0 Gm.	(o) 1000 0 cc.
(d) 2 0 Gm	(h) 16 0 Gm.	(l) gr. ix	(p) 1 qt.

3. Give the approximate metric equivalents of the following:

(a) 1 grain	(f) 1 fluidram	(k) 1 tablespoon
(b) 1 minim	(g) 1 ounce	(l) ½ tumblerful
(c) 15 grains	(h) 1 fluidounce	(m) 40 drops
(d) 15 minims	(i) 1 pint	(n) ¼ teaspoonful
(e) 1 dram	(j) 1 teacup	

Laboratory Suggestions

EQUIPMENT.—Apothecary measures, metric measures, household measures of various sizes and shapes, medicine droppers, water and oil.

1. Determine the metric or apothecary capacity of the household measures provided for you. Compare the sizes of three or four cups, glasses, teaspoons and tablespoons. Do you find any discrepancy? What can you say about the reliability of household measures?

2. With a medicine dropper, drop 20 drops of water into a minim glass. How many minims are there? Do the same with a water faucet instead of a medicine dropper. How many minims? Under what circumstances would a medicine dropper measure minims accurately?

3. Drop 20 drops of oil into a minim glass. How many minims? What factors determine the size of a drop?

The Preparation of Solutions and Doses

Solutions are made from pure drugs, stock solutions or tablets. *Pure drugs* are unadulterated substances in solid or liquid form. They are 100 per cent pure unless otherwise stated. Powders and crystalline substances such as boric acid, magnesium sulfate, carbolic acid crystals, etc., and a few liquids such as lysol, cresol, alcohol and glycerin are pure drugs.

Stock solutions are relatively strong solutions from which weaker solutions may be made. It is customary to have stock solutions on hand so that dilutions of various strengths may be made without the inconvenience and delay of weighing the pure drug. Examples of stock solutions commonly used are bichloride of mercury, phenol, potassium permanganate and magnesium sulfate.

Tablets containing a definite known quantity of drug may be used in making solutions. They also save the inconvenience of weighing the pure drug.

Methods of Making Solutions

There are two methods of making solutions, the *weight to weight* method and the *weight to volume* method. To be accurate, solutions should be made by the weight to weight method, according to which a given part by weight of the drug is dissolved in a given number of parts by weight of the solvent. A 1 per cent solution is made by this method so that it contains 1 part by weight of drug and 99 parts by weight of solvent in 100 parts by weight of solution.

By the weight to volume method, a given part by weight of drug is placed in the graduate and sufficient solvent is added to make the required amount of solution. This is the most practical method, and is the method most used in medicine and pharmacy.

Solutions of Pure Drugs

To prepare a solution of given strength of a pure drug, it is necessary to determine the amount of drug to use to make a given quantity of solution.

Examples: (1) Prepare 500 cc. of a 5 per cent solution of boric acid. *Five per cent* means that $\frac{5}{100}$ of the solution is boric acid. 500 cc. weigh 500 Gm. Hence $\frac{5}{100} \times 500$ (Gm.) = 25 Gm.

It is necessary to use 25 Gm. of pure drug. To prepare the solution, place 25 Gm. of boric acid in a graduate, add enough water to dissolve it and then add water up to 500 cc.

(2) How much drug is needed to make 1 ounce of a 1:25 carbolic acid solution?

The ratio 1:25 means that $\frac{1}{25}$ of the solution is carbolic acid. One ounce weighs 480 grains.

$$\frac{1}{25} \times 480 = 19.2 \text{ grains}$$

Dissolve 19.2 grains of carbolic acid in a quantity of water so that the total amount of solution measures one ounce.

Another method is:

The amount of drug is to the finished solution as the strength in per cent is to 100.

Amount of drug : the finished solution :: strength in % : 100.
The amount of drug is the unknown quantity or X.

$$X : 30 \text{ cc.} :: 4 : 100$$

$$100 X = 120$$

$$X = 1.2 \text{ Gm. of the drug.}$$

(3) Prepare a gallon of 1:1000 bichloride of mercury from tablets of $7\frac{1}{2}$ grains.

1:1000 means that $\frac{1}{1000}$ of the solution is drug.

1 gallon = 4000 cc. which weigh 4000 Gm.

$\frac{1}{1000} \times 4000$ Gm. = 4 Gm.; the amount of drug to be used.

4 Gm. = 60 gr.; $60 \div 7\frac{1}{2} = 8$ } the number of
or $7\frac{1}{2}$ gr. = 0.5 Gm.; $4 \div 0.5 = 8$ } tablets to be used.

Expressed decimally, the calculation would be:

$$4000 \text{ cc. of 1:1000} = \begin{cases} 4000 \times .001 = 4. \\ 7\frac{1}{2} = 0.5 \\ 4 \div 0.5 = 8 \text{ tablets.} \end{cases}$$

A second method is:

$$X : 4000 \text{ cc.} :: 1 : 1000$$

$$1000 X = 4000$$

$$X = 4 \text{ Gm. of the drug.}$$

Since each tablet contains $\frac{1}{2}$ Gm. of the drug, it would require 8 tablets.

To the amount of drug required should be added the amount of water sufficient to make the quantity of solution required.

Problems

Solutions from Pure Drugs

How would you prepare the following:

1. Twenty ounces of a 10 per cent carbolic acid solution?
2. One gallon of a 1:20 carbolic acid solution?
3. One liter of a 1 per cent saline solution?
4. One quart of a 1:25 boric acid solution?
5. One pint of a $\frac{1}{2}$ per cent cresol solution?
6. 500 c.c. of a 4 per cent solution of potassium chlorate?
7. How many $7\frac{1}{2}$ grain tablets of bichloride of mercury are required to make a liter of a 1:1,000 solution?
8. How many 5 grain tablets of sodium bicarbonate are necessary to make 500 cc. of a 5 per cent solution?
9. How many 0.2 Gm. tablets of potassium permanganate are needed to make 1 pint of a 1:2,000 solution?
10. Determine how many 3 grain tablets of ammonium chloride are required to make $\frac{1}{2}$ ounce of a 2 per cent solution.
11. Calculate the amount of silver nitrate required to make a liter of a 1:1,000 solution.
12. How much gentian violet is needed to make 3 ounces of a 1 per cent solution?
13. Determine the amount of glycerin necessary to make 100 c.c. of a 10 per cent solution.
14. How much boric acid is needed to make 1,500 cc. of a saturated solution?

15. Calculate the amount of potassium permanganate needed to make 1 quart of a stock solution (1:100).
16. How much acriflavine is needed to make 500 cc. of a 1:5,000 solution?
17. How much sodium chloride is needed to make 5 pints of a physiologic salt solution?
18. Determine the amount of carbolic acid crystals necessary to make 1 gallon of a 5 per cent solution.
19. Calculate the amount of lysol necessary to make 2 quarts of a 3 per cent solution.
20. Calculate the amount of mercurochrome needed to make 6 fluidounces of a 2 per cent solution.

Solutions From Stock Solutions

To prepare a solution from a stock solution, it is necessary to determine how much stock solution to use.

Example: Prepare one quart of a 2 per cent solution of formalin from a 40 per cent stock solution.

$$\frac{2}{100} \div \frac{40}{100} \times 1000 \text{ (cc.)} = \frac{2}{100} \times \frac{100}{40} \times \frac{50}{1000} = 50 \text{ cc.}$$

50 cc. of stock solution is poured into a graduate and sufficient water is added to make 1000 cc.

Example: Prepare 2500 cc. of a 1:8000 solution of bichloride of mercury from a 5 per cent solution:

$$\frac{1}{8000} \div \frac{5}{100} \times 2500 = \frac{1}{8000} \times \frac{100}{5} \times \frac{50}{2500} = \frac{59}{8} = 6\frac{1}{4} \text{ cc.}$$

6 $\frac{1}{4}$ cc. of stock solution is poured into the graduate, which is then filled to the 2500 cc. mark with water.

The rule for making the foregoing calculations is as follows: Divide the strength of the desired solution by the strength of the stock solution and multiply by the amount to be prepared. This determines the amount of stock solution necessary.

Another method is:

The amount of drug (stock solution) : finished solution :: ratio of strength of the two solutions.

As in example (1) above:

$$\begin{aligned} X : 1000 \text{ cc.} &:: 2:40 \\ 40 X &= 2000 \\ X &= 50 \text{ cc. stock solution} \end{aligned}$$

As in example (2) above:

5% may be expressed as 1-20

$X : 2500 \text{ cc.} :: 20:8000$

$8000 X = 50,000$

$X = 6\frac{1}{4} \text{ cc. of the stock}$
 solution to which should be added
 water sufficient to make 2500 cc.

Solutions From Stock Solutions

1. How much 25 per cent solution is needed to make the following and how would you prepare the solution?

3 ii of 1:5 solution
 1 qt. of 1:10 solution
 1 gal. of 1:20 solution
 500 cc. of 1:12½ solution
 3 x of 1:25 solution

1 pt. of 1:50 solution
 200 cc. of 1:5 solution
 1 3 of 1:10 solution
 1000 cc. of 1:8 solution
 500 cc. of 1:20 solution

2. How much 1:5 solution is needed to make:

100 cc. of 10 per cent solution
 500 cc. of 6 per cent solution
 1 pt. of 1:100 solution
 3 vi of 1:25 solution
 1 liter of 5 per cent solution

1 gal. of 1:20 solution
 200 cc. of 1:10 solution
 1 qt. of 1:1,000 solution
 500 cc. of 3 per cent solution
 6 oz. of 10 per cent solution

Solutions From Single Tablets

In this type of solution it is necessary to determine the amount of solvent in which to dissolve the tablet.

Example: Prepare a 5 per cent solution of sodium bicarbonate from a gr. v tablet.

Five per cent means that $\frac{5}{100}$ of the solution is drug— $\therefore \frac{5}{100}$ of solution = 5 gr.

\therefore Total solution = $5 \div \frac{5}{100} = 5 \times \frac{100}{5} = 100 \text{ gr.}$

100 gr. is the weight of 100 minims. Hence, to make the solution dissolve the tablet in 100 minims of solvent.

Or by the metric system:

5 grains = $5 \times 0.065 = 0.325 \text{ Gm.}$

$\frac{5}{100}$ of solution = 0.325 Gm.

$$\frac{325}{1000} \div \frac{5}{100} = \frac{65}{1000} \times \frac{100}{5} = \frac{65}{10} = 6.5 \text{ Gm.}$$

6.5 Gm. is weight of 6.5 cc.

Dissolve the tablet in 6.5 cc. of water.

The rule may be stated as follows: Divide the strength of the tablet by the strength of the desired solution.

Another method is:

The amount of drug : finished solution :: strength : 100.

As in the example above:

$$5 : X :: 5:100$$

$$5X = 500$$

$$X = 100 \text{ minims of solution.}$$

Doses From Stock Solutions

In some hospitals, drugs for hypodermic use are kept in solutions of various strengths. The strength is expressed either by percentage or as the number of minims which contain a certain dose, as $m x = \text{gr. } \frac{1}{8}$. The problem for the nurse is to determine how many minims of the stock solution contain the dose she is required to give. The same rule may be applied as in calculating doses from tablets; i.e., *Divide the required dose by the dose on hand*, in this case, the dose on hand being thought of as the fraction of a grain contained in one minim of the stock solution. Thus in a 1 per cent solution, one minim contains $\frac{1}{100}$ of a grain of the drug (since one minim weighs 1 grain). In a solution of which $m x = \text{gr. } \frac{1}{8}$, one minim contains $\frac{1}{80}$ of a grain of the drug.

1. Example.—How would you give strychnine sulfate gr. $\frac{1}{25}$ from a 1 per cent solution?

$$1 \text{ per cent} = \frac{1}{100} \text{ gr. in 1 minim}$$

$$\frac{1}{25} \div \frac{1}{100} = 4. \text{ Give 4 minims.}$$

or

$$\text{Amount of drug : finished solution} :: \text{strength} : 100.$$

$$\text{gr. } \frac{1}{25} : X :: 1:100$$

$$X = 4 m.$$

2. Example.—A bottle of strychnine sulfate is labeled $m x = \text{gr. } \frac{1}{30}$. How would you give gr. $\frac{1}{25}$?

$$\text{Since } m x = \text{gr. } \frac{1}{30}$$

$$m i = \text{gr. } \frac{1}{300}$$

$$\frac{1}{25} \div \frac{1}{300} = 12. \text{ Give 12 minims.}$$

or

$$X : \frac{1}{25} \text{ gr.} :: 10: \frac{1}{30}$$

$$\frac{1}{30} X = \frac{2}{3}$$

$$X = 12 m.$$

3. Example.—How would you give atropine sulfate gr. $\frac{1}{600}$ from a 1 per cent solution?

$$\frac{1}{150} \div \frac{1}{100} = \frac{2}{3} \text{ (minim)}$$

$$\text{The dose to be given is } \frac{2}{3} \text{ of a minim.}$$

or

$$\frac{1}{150} : X :: 1:100$$

$$X = \frac{2}{3} m.$$

As in example (2) above:

5% may be expressed as 1-20

$X : 2500 \text{ cc.} :: 20:8000$

$8000 X = 50,000$

$X = 6\frac{1}{4} \text{ cc. of the stock}$
 solution to which should be added
 water sufficient to make 2500 cc.

Solutions From Stock Solutions

1. How much 25 per cent solution is needed to make the following and how would you prepare the solution?

3 ii of 1:5 solution	1 pt. of 1:50 solution
1 qt. of 1:10 solution	200 cc. of 1:5 solution
1 gal. of 1:20 solution	1 $\bar{5}$ of 1:10 solution
500 cc. of 1:12 $\frac{1}{2}$ solution	1000 cc. of 1:8 solution
$\bar{3}$ x of 1:25 solution	500 cc. of 1:20 solution

2. How much 1:5 solution is needed to make:

100 cc. of 10 per cent solution	1 gal. of 1:20 solution
500 cc. of 6 per cent solution	200 cc. of 1:10 solution
1 pt. of 1:100 solution	1 qt. of 1:1,000 solution
$\bar{5}$ vi of 1:25 solution	500 cc. of 3 per cent solution
1 liter of 5 per cent solution	6 oz. of 10 per cent solution

Solutions From Single Tablets

In this type of solution it is necessary to determine the amount of solvent in which to dissolve the tablet.

Example: Prepare a 5 per cent solution of sodium bicarbonate from a gr. v tablet.

Five per cent means that $\frac{5}{100}$ of the solution is drug— $\therefore \frac{5}{100}$ of solution = 5 gr.

\therefore Total solution = $5 \div \frac{5}{100} = \bar{5} \times \frac{100}{\bar{5}} = 100 \text{ gr.}$

100 gr. is the weight of 100 minims. Hence, to make the solution dissolve the tablet in 100 minims of solvent.

Or by the metric system:

5 grains = $5 \times 0.065 = 0.325 \text{ Gm.}$

$\frac{5}{100}$ of solution = 0.325 Gm.

$$\frac{325}{1000} \div \frac{5}{100} = \frac{65}{1000} \times \frac{100}{\bar{5}} = \frac{65}{10} = 6.5 \text{ Gm.}$$

6.5 Gm. is weight of 6.5 cc.

Dissolve the tablet in 6.5 cc. of water.

The rule may be stated as follows: Divide the strength of the tablet by the strength of the desired solution.

Another method is:

The amount of drug : finished solution :: strength : 100.

As in the example above:

$$5 : X :: 5:100$$

$$5X = 500$$

$$X = 100 \text{ minims of solution.}$$

Doses From Stock Solutions

In some hospitals, drugs for hypodermic use are kept in solutions of various strengths. The strength is expressed either by percentage or as the number of minims which contain a certain dose, as $\text{m x} = \text{gr. } \frac{1}{8}$. The problem for the nurse is to determine how many minims of the stock solution contain the dose she is required to give. The same rule may be applied as in calculating doses from tablets; i.e., *Divide the required dose by the dose on hand*, in this case, the dose on hand being thought of as the fraction of a grain contained in one minim of the stock solution. Thus in a 1 per cent solution, one minim contains $\frac{1}{100}$ of a grain of the drug (since one minim weighs 1 grain). In a solution of which $\text{m x} = \text{gr. } \frac{1}{8}$, one minim contains $\frac{1}{80}$ of a grain of the drug.

1. **Example.**—How would you give strychnine sulfate gr. $\frac{1}{25}$ from a 1 per cent solution?

$$1 \text{ per cent} = \frac{1}{100} \text{ gr. in 1 minim}$$

$$\frac{1}{25} \div \frac{1}{100} = 4. \text{ Give 4 minims.}$$

or

$$\text{Amount of drug : finished solution} :: \text{strength} : 100.$$

$$\text{gr. } \frac{1}{25} : X :: 1:100$$

$$X = 4 \text{ m.}$$

2. **Example.**—A bottle of strychnine sulfate is labeled $\text{m x} = \text{gr. } \frac{1}{30}$. How would you give gr. $\frac{1}{25}$?

$$\text{Since } \text{m x} = \text{gr. } \frac{1}{30}$$

$$\text{m i} = \text{gr. } \frac{1}{300}$$

$$\frac{1}{25} \div \frac{1}{300} = 12. \text{ Give 12 minims.}$$

or

$$X : \frac{1}{25} \text{ gr.} :: 10 : \frac{1}{30}$$

$$\frac{1}{30} X = \frac{2}{3}$$

$$X = 12 \text{ m.}$$

3. **Example.**—How would you give atropine sulfate gr. $\frac{1}{500}$ from a 1 per cent solution?

$$\frac{1}{500} \div \frac{1}{100} = \frac{2}{5} \text{ (minim)}$$

The dose to be given is $\frac{2}{5}$ of a minim.

or

$$\frac{1}{500} : X :: 1:100$$

$$X = \frac{2}{5} \text{ m.}$$

To obtain a fraction of a minim dissolve one minim of the stock solution in a number of minims of water so that the total number of minims of the new solution can be divided evenly by the denominator, and take the amount indicated by the fraction. To prepare the above dose, dissolve one minim of stock solution in 14 minims of water. This gives a total of 15 minims of which $\frac{2}{3}$ or 10 minims contain atropine sulfate gr. $\frac{1}{150}$.

4. Example.—How would you give gr. $\frac{1}{60}$ strychnine sulfate from a solution of which $\text{m} \text{ v} = \text{gr. } \frac{1}{30}$?

$$\text{m} \text{ v} = \text{gr. } \frac{1}{30}$$

$$\text{m} \text{ i} = \text{gr. } \frac{1}{150}$$

$$\frac{1}{60} \div \frac{1}{150} = 2\frac{1}{2}$$

The dose to be given is $2\frac{1}{2}$ minims.

To give this dose, obtain the fractional part by first dissolving one minim of stock solution in 19 minims of water, which gives 20 minims, and taking $\frac{1}{2}$ of this or 10 minims. To these 10 minims, add two minims of stock solution. The solution obtained contains $2\frac{1}{2}$ minims of stock solution.

Problems

Doses from Stock Solutions

- How would you calculate the following doses:
 - Strychnine sulfate gr. $\frac{1}{40}$, gr. $\frac{1}{20}$, gr. $\frac{1}{100}$, gr. $\frac{1}{60}$, gr. $\frac{1}{120}$ from a 1 per cent solution?
 - Atropine sulfate gr. $\frac{1}{150}$, gr. $\frac{1}{160}$, gr. $\frac{1}{80}$, gr. $\frac{1}{200}$, gr. $\frac{1}{45}$ from a 2 per cent solution?
 - Eserine salicylate gr. $\frac{1}{80}$, gr. $\frac{1}{40}$, gr. $\frac{1}{60}$, gr. $\frac{1}{100}$ from a $\frac{1}{2}\%$ solution?
 - Strychnine sulfate gr. $\frac{1}{30}$, gr. $\frac{1}{60}$, gr. $\frac{1}{120}$, gr. $\frac{1}{100}$, gr. $\frac{1}{150}$ from a 1:200 solution?
 - Morphine sulfate gr. $\frac{1}{4}$, gr. $\frac{1}{8}$, gr. $\frac{1}{10}$, gr. $\frac{1}{20}$ from a 1:25 solution?
 - Pilocarpine nitrate gr. $\frac{1}{15}$, gr. $\frac{1}{20}$, gr. $\frac{1}{24}$, gr. $\frac{1}{8}$, gr. $\frac{1}{12}$ from a solution of which $\text{m} \text{ x}$ contain gr. $\frac{1}{12}$?
 - Cocaine hydrochloride gr. $\frac{1}{6}$, gr. $\frac{1}{8}$, gr. $\frac{1}{12}$, gr. $\frac{1}{2}$, gr. $\frac{1}{16}$ from a solution of which $\text{m} \text{ v}$ contain gr. $\frac{1}{4}$?
 - Strychnine sulfate gr. $\frac{1}{15}$, gr. $\frac{1}{30}$, gr. $\frac{1}{60}$, gr. $\frac{1}{80}$, gr. $\frac{1}{100}$ from a solution of which $\text{m} \text{ x}$ contain gr. $\frac{1}{60}$?
- Give caffeine sodio-benzoate gr. iv from a 25 per cent solution.
- Give potassium iodide gr. xv from a 50 per cent solution.
- How would you prepare codeine sulfate gr. $\frac{1}{2}$ from a 5 per cent solution?
- How would you prepare atropine sulfate gr. $\frac{1}{120}$ when each ten minims of the stock solution contain gr. $\frac{1}{30}$?
- If $\text{m} \text{ xx}$ of a solution contain gr. $\frac{1}{4}$ of morphine sulfate, explain how you would give a $\frac{1}{12}$ grain dose.
- If you have tablets of 0.4 Gm. on hand, how would you give 0.3 Gm., 0.2 Gm., 0.8 Gm., 0.6 Gm., 2.0 Gm.?

8. From Magendie's solution of morphine (1-30) give gr. $\frac{1}{6}$, gr. $\frac{1}{4}$, gr. $\frac{1}{3}$, gr. $\frac{1}{10}$, gr. $\frac{1}{8}$.
9. From a 0.25 per cent solution of aconitine how would you give gr. $\frac{1}{400}$, gr. $\frac{1}{300}$, gr. $\frac{1}{600}$?
10. If 10 minims of a solution of morphine sulfate contain gr. $\frac{1}{8}$, how many minims are required to give gr. $\frac{1}{12}$, gr. $\frac{1}{16}$, gr. $\frac{1}{24}$, gr. $\frac{1}{6}$, gr. $\frac{1}{4}$?

Calculation of Fractional Doses

Doses and Tablets.—Potent drugs, such as the alkaloids and glucosides, usually come in tablets of definite doses designed for hypodermic use. If the dose which the nurse is called upon to give is not the same as that of the tablet, it is necessary for her to calculate how many tablets or what part of one tablet will contain the required dose.

Example.—The physician orders strychnine sulfate gr. $\frac{1}{30}$ and the tablets on hand are gr. $\frac{1}{60}$. It is obvious that 2 tablets will be required; or writing out the arithmetic involved:

$$\frac{1}{30} \div \frac{1}{60} = 2$$

Example.—The physician orders strychnine sulfate gr. $\frac{1}{60}$ and the tablets on hand are gr. $\frac{1}{30}$.

$$\frac{1}{60} \div \frac{1}{30} = \frac{1}{2}$$

One-half of the stock tablet must be given.

Example.—An order is written for strychnine sulfate gr. $\frac{1}{40}$ and the tablets on hand are gr. $\frac{1}{60}$.

$$\frac{1}{40} \div \frac{1}{60} = \frac{3}{2} \text{ or } 1\frac{1}{2}$$

One whole tablet and one-half of another are required.

From the above examples, the following rule may be deduced:
To give a fractional dose from a stock tablet, divide the required dose by the dose on hand. The result will be the fraction of the stock tablet to be given.

Technic.—Dissolve the stock tablet in a number of minims which can be divided evenly by the denominator of the fraction and give the fraction of this solution. Thus, if $\frac{1}{2}$ of a tablet is to be given, dissolve the tablet in twenty minims of water and give $\frac{1}{2}$ or 10 minims of the solution thus obtained. This dose will contain one-half the original tablet.

Problems

Dosage from Tablets

1. How would you calculate and prepare the following doses:
 - a. Atropine sulfate gr. $\frac{1}{120}$ from tablets of gr. $\frac{1}{100}$?
 - b. Thyroxin gr. $\frac{1}{150}$ from gr. $\frac{1}{100}$ tablets?

- c. Strychnine sulfate gr. $\frac{1}{60}$ from gr. $\frac{1}{15}$ tablets?
 - d. Cocaine hydrochloride gr. $\frac{1}{4}$ from tablets of $\frac{1}{2}$ grain?
 - e. Pilocarpine hydrochloride gr. $\frac{1}{5}$ from tablets of gr. $\frac{1}{8}$?
 - f. Atropine sulfate gr. $\frac{1}{50}$ from tablets of gr. $\frac{1}{100}$?
 - g. Strychnine sulfate gr. $\frac{1}{30}$ from tablets of gr. $\frac{1}{60}$?
 - h. Heroin hydrochloride gr. $\frac{1}{10}$ from tablets of gr. $\frac{1}{20}$?
 - i. Eserine salicylate gr. $\frac{1}{10}$ from tablets of gr. $\frac{1}{20}$?
 - j. Aconitine gr. $\frac{1}{10}$ from tablets of gr. $\frac{1}{20}$?
2. From tablets of strychnine sulfate, gr. $\frac{1}{30}$, how would you prepare: gr. $\frac{1}{20}$, gr. $\frac{1}{60}$, gr. $\frac{1}{40}$, gr. $\frac{1}{100}$?
 3. From tablets of hyoscyamine hydrobromide gr. $\frac{1}{100}$ how would you prepare: gr. $\frac{1}{80}$, gr. $\frac{1}{20}$, gr. $\frac{1}{150}$, gr. $\frac{1}{200}$?
 4. From tablets of cocaine hydrochloride gr. $\frac{1}{4}$, prepare the following doses: gr. $\frac{1}{8}$, gr. $\frac{1}{6}$, gr. $\frac{1}{10}$, gr. $\frac{1}{12}$, gr. $\frac{1}{24}$.
 5. (a) Give atropine sulfate gr. $\frac{1}{40}$ from tablets of gr. $\frac{1}{100}$.
 (b) How much of a gr. iii tablet of sodium cacodylate is necessary to give a dose of gr. ii?
 (c) What part of a gr. $\frac{1}{60}$ tablet is needed to give a gr. $\frac{1}{100}$ dose?
 (d) How would you prepare a gr. $\frac{1}{120}$ dose of digitoxin from a gr. $\frac{1}{100}$ tablet?
 (e) How would you prepare a gr. $\frac{1}{250}$ dose of nitroglycerin from tablets of gr. $\frac{1}{60}$?

Dosage by Age

Age is an important element in dosage. Weight also is important. But other factors, such as obesity, must be considered. Children have more central nervous system for their weight than adults; and are, therefore, more susceptible to drugs that act on the nervous system. A dose of a narcotic, especially of the opium series, should be given in smaller doses than the weight calls for. This is the usual statement by practitioners. There is, however, some question about its validity.

A good simple rule of dosage by age is the following:

At 20 yr.	give the adult dose
At 10 yr.	$\frac{1}{2}$ the adult dose
At 5 yr.	$\frac{1}{4}$ the adult dose
At $2\frac{1}{2}$ yr.	$\frac{1}{8}$ the adult dose
At 1 yr.	$\frac{1}{12}$ the adult dose
At $\frac{1}{2}$ yr.	$\frac{1}{24}$ the adult dose

Between these ages, a little more than the smallest dose nearest to their age, but less than the greater dose nearest to their age.

Other rules for estimation of dosage for children:

$$\text{Fried's Rule for infants: Adult dose} \times \frac{\text{age in months}}{150}$$

$$\text{Bastedo's Rule: Adult dose} \times \frac{\text{age} + 3}{30}$$

$$\text{Young's Rule: Adult dose} \times \frac{\text{age}}{\text{age} + 12}$$

Problems

Doses for Children

1. If the adult dose of morphine sulfate is 0.005 Gm., calculate the dose for a nine-year-old child.
2. If the adult dose of Fowler's solution is \mathfrak{M} iii, what is the dose for a child of six years?
3. How much compound licorice powder would you give to a child of ten years? The adult dose is 3 i.
4. How much tincture of digitalis would be given to an eight-year-old child, the adult dose being \mathfrak{M} x?
5. The adult dose of santonin is 1 gr.; what is the dose for a five-year-old child?
6. The adult dose of castor oil is 16 cc. How much would you give to a child of seven years?
7. How much castor oil would you give to a ten-month-old infant if the adult dose is 16 cc.?
8. What is the dose of calomel for a child of three years, the adult dose being 0.3 Gm.?
9. If the adult dose of a drug is 10 grains, what is the dose for a five-year-old child?
10. If the adult dose of a drug is gr. $\frac{1}{4}$, what is the dose for a child of ten years?

CHAPTER VI

THE ADMINISTRATION OF MEDICINES

The administration of medicines is one of the most important duties of the nurse. It is her responsibility to see that the doctor's orders are carried out accurately, promptly, and in such a way as to insure the best results for the patient. To be able to do this she needs to know something about the physical and chemical properties of the drug, its local and systemic action in the body, the maximum and minimum dosage, the factors which modify the dosage, the condition of the patient, the therapeutic effects desired and the best ways to attain them, and the symptoms which indicate the attainment of these effects or more important still, the failure to attain them and the presence of untoward results due to idiosyncrasy or cumulative poisoning. Moreover, she must realize the seriousness of her responsibility and be conscientious in every detail that will tend to make her ministrations more accurate and effective.

Major Channels of Drug Administration.—In order that the nurse have some appreciation of how therapeutic effects of drugs are secured it is important to know how drugs should be administered to secure optimum effects. As a rule, we recognize two main types of administration: *local*, where the action of the drug is confined to the site of application, and *systemic*, where the drug is absorbed into the blood and is distributed throughout the body. Some drugs are administered locally but are absorbed and therefore exert a systemic effect.

I. LOCAL ADMINISTRATION

1. Applications to the Skin and Wounds

Medications are applied to the skin chiefly as antiseptics and astringents in the form of aqueous solutions, wet dressings, liniments, ointments, cerates, poultices, plasters, and dusting powders. (a) Medicines are used in wounds for the same purposes, most commonly in the form of continuous irrigation or wet dressing or impregnated gauze, although ointments and dusting powders are also used. (b) Wet dressings must be kept moist by frequent changing, which also serves to drain the secretions and keep the wound dry. Certain drugs like iodoform are readily absorbed from wounds

and patients must be carefully watched for signs of systemic poisoning. (c) Liniments are usually applied with friction which aids penetration. They may be applied on flannel which keeps the skin warm and prevents evaporation of the liniment.

(d) Ointments are the best means of applying remedies for a prolonged effect. The fatty substances which form their base dissolve readily but do not evaporate and thus prolong the local effect of the drug.

The ointment should be applied on flannel or cotton cloth and should be changed once a day. Ointments should not be used on discharging wounds as they prevent free drainage of the secretions. Cerates are administered like ointments. The method of administering drugs through the skin is known as endermic medication.

(e) Poultices and plasters are used generally as anodynes (to relieve pain), or as (f) counterirritants (to redden the skin or cause blisters). The medicinal substance is usually diluted with flour until the desired strength is obtained, water is added to form a paste, which is then wrapped in a piece of gauze or cotton cloth and applied to the site indicated. Plasters should be moistened before application.

The duration of application of poultices and plasters depends upon the effect desired. Usually ten to twenty minutes are necessary to produce a rubefacient action, and longer for the formation of a blister. A flaxseed poultice is kept on as long as the heat is retained; a mercury plaster may be kept on for days.

(g) Dusting powders are dusted over the surface of a wound or ulcer, or on the skin.

2. Application to Mucous Membranes

Applications to mucous membranes are chiefly antiseptic and astringent in character. To medicate the mucous membranes of the mouth and throat, drugs are used in aqueous solutions as (a) *gargles, sprays or mouth washes*, and as lozenges and troches; on nasal mucous membranes they are applied by (b) *swabbing, spraying and douching*. (c) To produce only local effects on the mucous membranes of the stomach, drugs must be either insoluble in the fluids of the stomach or not absorbable into the blood stream. A drug that is absorbable may be introduced into the stomach for local action and removed again by means of the stomach tube before action can take place. (d) To insure local action in the intestine, drugs have to be given in the form of pills coated with keratin or salol or as powders enclosed in capsules of those substances, which pass through the acid secretions of the stomach undissolved, but are soluble in the alkaline

secretions of the intestine. (e) Drugs are introduced into the rectum in the form of enemas and irrigations, and suppositories.

(f) The mucous membranes of the genitourinary tract may be medicated in the following ways: (1) the urethra with injections, irrigations or (2) urethral suppositories or bougies; (3) the bladder with irrigations and instillations; (4) the vagina with douches, tampons and suppositories; and (5) the uterus with douches and irrigations.

(g) Medicated steam and inhalations of fumes from burning drugs are employed to treat catarrhal and other inflammatory conditions of the respiratory tract. Nebulae may be sprayed on the irritated mucosa. See p. 331.

(h) Drops may be instilled into eye, nose or ear.

(i) When a drug is applied locally to a wound or cavity by blowing it into the cavity, it is said to be administered by insufflation. Antiseptics and anesthetics are sometimes given this way.

II. ADMINISTRATION FOR SYSTEMIC EFFECTS

Drugs given for a systemic effect must enter the blood stream. The method of administration of such substance depends upon the rapidity with which action is desired, the nature and amount of the drug to be given, and the condition of the patient.

- | | |
|------------------|--------------------|
| 1. By mouth | 6. Parenterally |
| 2. By rectum | a) Subcutaneously |
| 3. By inhalation | b) Intramuscularly |
| 4. Byunction | c) Intravenously |
| 5. Sublingually | d) Intraspinally |

1. By Mouth

The oral channel of drug administration is usually the safest, most economical, and most convenient way of giving medicines. Hence they should be given this way unless some very distinct advantage is to be obtained by a different route. Even if the patient is unable to swallow, the medication may be administered by stomach or nasal tube or by tube administration into some part of the bowel.

If, however, the drug causes gastrointestinal distress, or if absolute rest of the alimentary organs is essential, or if the drug is subject to change by the digestive enzymes, then the burden of absorption must be assumed by some other part of the body. In case of emergency or shock when circulation is sluggish and absorption therefore uncertain, more rapidly acting modes of administration may be essential.

Minor disadvantages encountered in oral administration have to do with taste and smell of certain drugs. A few drugs are known to be harmful to the teeth and should be administered well diluted through a glass tube or straw. Gelatin capsules have a wide use when drugs are disagreeable to take. The taste should be made as pleasant as possible, especially when the drug must be given over a long period of time. Tablets and pills should be crushed before giving them to children.

Absorption cannot take place until the drug has been dissolved in some fluid, either before administration or afterward in the fluids of the stomach or intestines. The greater the amount of solvent, the more readily will the drug be absorbed. Absorption can be aided therefore by giving drugs well diluted preferably with water which is the best solvent and the one from which drugs are most readily absorbed. Unless otherwise ordered, all drugs except oils or cough syrups are given with water. Oils are saponified and go into solution in the intestine. Drugs given by mouth are for the most part absorbed from the mucosa of the small intestine. There is a relatively small amount of absorption from the mucosa of the stomach.

Absorption from the alimentary tract is always subject to a number of irregularities and is therefore never as certain as when the drug is given by injection.

2. By Rectum

Drugs are introduced into the rectum in soluble form or in suppository form to produce local as well as systemic effect. Administration for absorption and systemic effect will be considered here.

The rectum is capable of considerable absorption, provided it is empty and not excessively irritable. If the rectum is distended with feces, it should be emptied with an evacuant enema before the medication is given. If the rectum is excessively irritable, it may be necessary to administer the drug through some other channel since the natural response of this organ is to expel content rather than retain it.

Rectal administration can be used to advantage when the stomach is nonretentive, when the medicine has an objectionable odor or taste, and when the medication is capable of being changed by the digestive juices. Rectal administration is a fairly convenient and safe method of giving drugs when the oral route cannot be used. The rate of absorption is, however, rather uncertain. In the event

that some of the drug is expelled, it is difficult to determine how much of the drug has been retained. Some authorities advocate increasing the dosage over that of an oral medication while others believe it may be decreased, provided the rectum has been well evacuated prior to the administration of the medicine.

3. By Inhalation

The respiratory tract offers an enormous surface of absorbing epithelium. If the drug is volatile and capable of being absorbed and if there is more of it in the inspired air than in the blood, a large amount of the drug may be absorbed with great rapidity and may produce an almost immediate effect. Drugs administered by inhalation produce effects almost as soon, if not as rapidly, as those administered by intravenous injection. This fact is of great value in emergency situations. Amyl nitrite, anesthetics, smelling salts, oxygen, and carbon dioxide are examples of volatile substances given by inhalation, for systemic effects.

4. By Inunction

Certain drugs are rubbed into the skin for a systemic effect. They are usually applied in the form of an ointment composed of some fatty base such as cocoa butter or olive oil in which the drug is mixed. The active ingredient of the ointment when rubbed into the hair follicles and sweat glands of the skin, slowly finds its way into the blood stream.

The amount of absorption and consequently the therapeutic effects derived, depend upon the condition of the skin, the briskness of the blood circulation, the extent of the surface treated, and the thoroughness with which the ointment is applied.

Prior to application the skin should be thoroughly washed with warm water and soap. The ointment should be rubbed in with a circular movement of the palm of the hand until it seems to have disappeared. The sites of application should be where the skin is thin, i.e., the sides of the chest and inner aspect of the arms, legs, and groin.

Mercurial ointment is an example of a preparation still effectively employed and applied by inunction. It is used in the treatment of syphilis. As this ointment is irritating and poisonous a limited amount is prescribed and it is applied to small surfaces. It is never applied to the same area on successive days but the above mentioned sites are used in rotation. This is called a *course of applications*.

When applying mercurial ointment, a nurse should always wear a glove; otherwise, she may absorb some of the drug herself and get poisonous effects.

5. Sublingually

Drugs held under the tongue are rapidly absorbed, and by this method one avoids destruction by digestion and by the liver. Liquids may be dropped on a pellet of cotton and held under the tongue. Tablets of nitroglycerin are usually administered sublingually. The number of drugs given this way is rather limited. The drug must be highly soluble in the mouth and the nurse must gain the cooperation of the patient.

6. Parenterally

The administration of medicinal substances into the body by routes other than by the alimentary canal (rectal or oral) is known as parenteral administration. This method has come to include all the ways by which medications are given by a needle directly into the tissues, namely, subcutaneous, intramuscular, intravenous, intraspinal, intrathecal, and intraperitoneal injection. Although the regulations in hospitals differ, nurses are usually responsible for the technic of subcutaneous and intramuscular injections, while the doctor assumes responsibility for the other parenteral methods of drug administration.

Drugs given parenterally should be readily soluble, should withstand sterilization, should be rapidly absorbed, and should not cause pain or irritation at the site of injection.

a. Subcutaneous Injection.—Small amounts of a drug are given subcutaneously by means of a hypodermic syringe and needle. The needle is inserted through the skin at an angle of 45 degrees. The favorite sites of injection are those of the outer surfaces of the arms and forearms or thighs. In these locations there are fewer large blood vessels and sensation is somewhat less keen than on the inner aspects of the extremities. To avoid pain, a sharp, clean needle should always be used and it should be inserted quickly and the solution injected slowly. The site of injection should then be gently massaged.

Drugs are given hypodermically when prompt action is desired or when for any reason it is inadvisable or impossible to give the drug by mouth. Only those drugs can be used which are readily dissolved and absorbed, and which can be given in concentrated form. Any considerable amount given in this way would cause undue pressure and consequent injury to the tissues.

Irritating drugs cannot be given subcutaneously since they may give rise to abscess formation. They are usually given intramuscularly or even intravenously.

The administration of large amounts of fluid into the subcutaneous tissues is said to be given by hypodermoclysis. The fluid is directed into the tissue just under the breasts or in the groin where there is considerable loose connective tissue which is capable of distention and absorption. Isotonic salt solution or glucose solutions are commonly administered this way. While this is an excellent method of restoring body fluids it can be overdone. It is possible for the tissues to become waterlogged, resulting in a num-

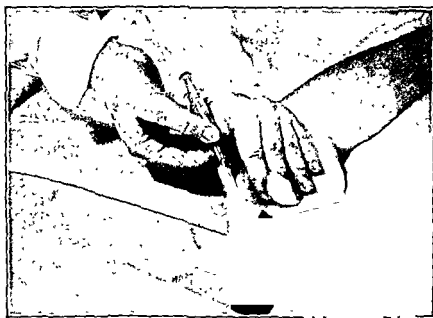


Fig. 4.—Subcutaneous or hypodermic injection. As the needle enters the tissues it should be at an angle of approximately 45 degrees. The medication is deposited into the subcutaneous tissues.

ber of undesirable reactions. The rapidity of absorption depends on the rate of administration and the state of fluid balance in the body as well as on the briskness of blood circulation.

Intradermal injections, or injections into the skin but which do not penetrate the true skin, are sometimes used in vaccinations.

b. **Intramuscular Injection.**—The deposit of a medicine into the muscle tissue of the body constitutes an intramuscular injection. Muscles suited to this type of drug administration are those of the buttocks, thigh, back, and arm.

Intramuscular injection is the method of choice when prompt absorption is desired and the drug is too irritating to be given by the

subcutaneous route. Drugs may be dissolved or suspended in oil and then given intramuscularly. This promotes slow even absorption.

The technic of intramuscular injection is taught elsewhere but a number of points bear repetition or emphasis here. The skin should be stretched rather than picked up in a fold and the intramuscular needle which is usually about $1\frac{1}{2}$ inches long is inserted more or less perpendicularly. It is then necessary to pull up on the plunger and aspirate for a few seconds to make certain that the needle has not entered a vein. If blood is aspirated, the needle should be withdrawn and the procedure repeated in an area away from the previous puncture.



Fig. 5.—Intramuscular injection. The needle is thrust vertically into the tissues through the skin, subcutaneous tissue, and into the muscle tissue.

If the patient is up and about, the preferable site of injection is the buttock. The buttock is divided into four parts and the injection is given into the upper outer quadrant. It is important to solicit the cooperation of the patient and have as much muscular relaxation as possible. The placement of a pillow under the legs just below the knees helps to promote relaxation and thus helps to prevent leakage along the track of the needle.

Just before the needle is inserted it is desirable for the nurse to press firmly the skin and soft tissue of the buttock downward in the direction of the patient's heels. This can be done with the flat of the left hand. The needle is then inserted at approximately a 90°

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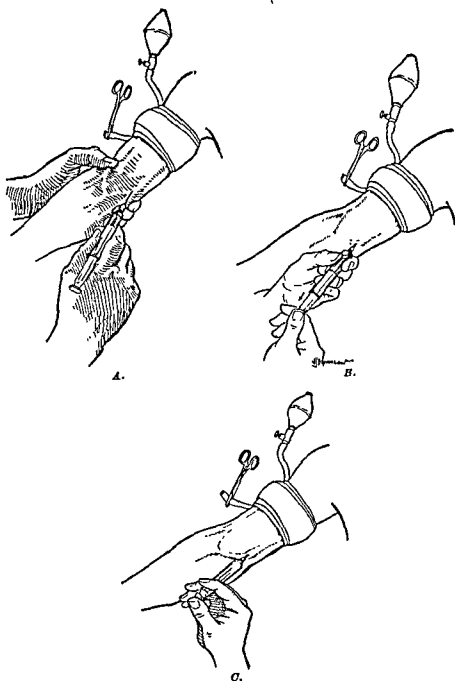


Fig. 6.—The technic of intravenous administration of solutions of drugs. (From Clendening: *Methods of Treatment*.)

A. Shows tourniquet in place and the operator about to plunge the needle through the skin into the vein. The tourniquet is improvised from the cuff of a blood pressure apparatus. This is the best form of tourniquet possible. The bulb has been squeezed up so that the veins are distended.

B. The needle is in the vein as shown by the blood flowing into the syringe. The air is now led out of the cuff of the tourniquet and the solution slowly introduced.

C. The solution has been completely introduced. The syringe is empty. The needle is now withdrawn from the vein and the tourniquet is removed.

angle *but it should not be inserted up to the hub*. The medicine should be injected *very slowly*. The needle is then swiftly withdrawn, and the soft tissues which have been drawn downward are pushed back to their normal position. *Gentle massage of the area should follow*.

When injection is made into the thigh muscles, the area of the vastus externus muscle or just below it is the area of choice. The skin is least sensitive there and absorption seems to be better. The triceps or deltoid muscles of the arm are the muscles of choice in the upper extremities.

To prevent excessive scar formation, no two injections should be given in the same spot during a course of treatments. When the injections are given into the buttocks, they should be given on one side and then on the other.

Liver extract, whole blood, diphtheria, and tetanus antitoxin are examples of preparations given by intramuscular injection.

The disadvantages sometimes encountered when medicines are given by the intramuscular route lie in the danger of injecting the drug into a vein, in which case absorption may be dangerously rapid, or the danger of accidentally breaking the needle. The latter might be caused by striking a bone or by a sudden movement on the part of the patient, or the needle might be defective. If the needle accidentally breaks, the nurse should not remove her hand from the area where pressure is exerted but should tell the patient to lie *very* quietly. It may be possible to get hold of the end of the needle or else call for help, *but the tissue should be held firmly until the doctor arrives*. A small incision will then expose the needle, whereas if pressure has been removed from the buttock an extensive operation may be necessary to recover the needle.

c. **Intravenous Injection.**—When an immediate effect is desired or when for any reason the drug cannot be injected into the other tissues, it may be given directly into a vein as an injection or infusion. The technic of this method requires skill and perfect asepsis, and the drug must be highly soluble and capable of withstanding sterilization. It should therefore be used carefully and not too frequently. The method is of great value in emergencies. The dose and amount of absorption can be determined with accuracy, although the rapidity of absorption and the fact that there is no recall once the drug has been given constitute dangers which are important.

A vein which is normally distended with blood is much easier to enter than a partially collapsed vein. If a vein of the arm has been chosen, a tourniquet is drawn tightly around the middle of the arm to distend the vein, the air is expelled from the syringe, and the needle is introduced, pointing upward toward the heart. A few drops of blood are aspirated into the syringe to make sure the needle is in the vein; the tourniquet is then removed and the solution is injected very slowly. The needle, syringe and solution must be sterile and the hands of the doctor and nurse and the skin of the patient at the point of insertion of the needle must be clean. Intravenous injection is employed when immediate action is necessary, when the drug is too irritating to be injected into the other tissues or when the circulation is so poor that absorption is much retarded.

In intravenous infusion a larger amount of fluid is usually given, varying from one to five pints, and the method differs somewhat. The solution is made to flow by gravity or siphonage from a graduated glass flask through a rubber tubing, connecting tip and needle into the vein.

Infusions are most commonly given to relieve tissue dehydration, to restore depleted blood volume, to dilute toxic substances in the blood and tissue fluids, and to combat acidosis.

During the administration of the intravenous infusion the patient must remain very quiet to prevent the displacement of the needle. The fluid must be given very slowly, however, to prevent reaction or loss of important constituents by way of the kidney. Ordinarily two to three hours are required for every 1000 c.c. of fluid.

Solutions Used.—Sodium chloride (0.9%) solution, commonly known as physiologic salt solution, is the fluid of choice for intravenous infusion to relieve any case of dehydration which is not complicated by acidosis. Physiologic salt solution may be sterilized by boiling, and it is isotonic with normal body fluids.

Solutions of soda bicarbonate are used in the treatment of acidosis. They are more difficult to sterilize than physiologic salt solution because the bicarbonate tends to break down and liberate carbon dioxide when the solution is heated.

Five and ten per cent glucose solutions are frequently administered and are of value because they provide a means of administering water, salts, and a substance which can be oxidized to liberate energy. A concentration of 5.5 per cent is approximately isotonic with normal body fluids.

From this standpoint it is one of the least safe methods of administration. However, irritating drugs may sometimes be given this way when they could not be tolerated by any other method. This is possible because they are rapidly diluted with the blood and the vessel wall is relatively insensitive.

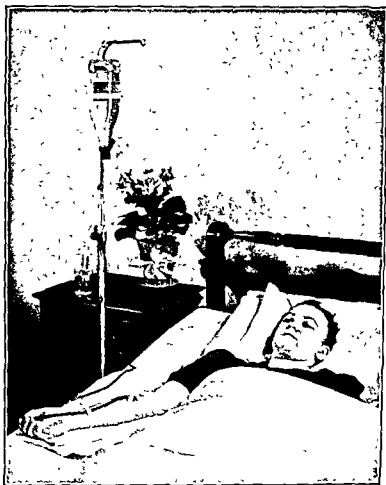


Fig 7—Intravenous infusion

In intravenous injection a comparatively small amount of solution is given by means of a syringe. The drug is dissolved in a suitable amount of normal saline or other isotonic solution. The injection is made usually into the median basilic or the median cephalic vein at the bend of the elbow. However, any vein may be used which is accessible. Factors which determine the choice of a vein are related to the thickness of the skin over the vein, the closeness of the vein to the surface, and the presence of a firm support under the vein (bone).

3. The medicines should be arranged in the closet alphabetically in some such order as the following:
 - (a) Substances for external use should be kept together, solids and liquids in separate compartments.
 - (b) Substances for internal use should be kept together, solids and liquids in separate compartments.
 - (c) All potent drugs, such as morphine, strychnine, etc., usually given hypodermically, should be in a separate compartment.
 - (d) All poisons should be labelled "Poison." They should be kept separately in bottles differentiated by color, shape, or rough surface.
 - (e) As far as possible drugs used for a similar action should be grouped together, i.e., cathartics, sedatives, etc.
 - (f) Oils should be kept in a cool place, since they readily decompose.
 - (g) Sera and vaccines should be kept in the ice box.
4. The closet should be well supplied with the drugs likely to be needed, but should not be overstocked.
5. The contents of the closet should be examined every day and any change in color, odor or consistency of a drug should be reported.
6. Bottles should be securely corked and labelled. Labels should be printed and always clean. No nurse, however, should alter or change a label—that is the duty of the pharmacist.
7. Closets, shelves, bottles, etc., should be immaculately clean and orderly. Bottles should be of a uniform size and shape, and arranged so that each label is plainly visible.

The Physician's Order Book

On some hospital wards there is a book in which the physician writes his orders. In other hospitals the order may be written on the patient's chart. Except in an extreme emergency, a nurse should never give a medicine unless the order for it is first written and signed by the physician. If an emergency makes this impossible, the order should be written and signed later.

Nurses should look at the orders frequently because a doctor may write an order without calling the attention of a nurse to it. If there is the least doubt about a patient's medication, there is only one good place to check it and that is the doctor's original written order.

Solutions containing acacia are used primarily to increase blood volume in circulatory shock. This substance serves, temporarily at least, to replace serum proteins which have escaped from injured capillary walls. Acacia is not a U. S. P. drug.

A number of commercial solutions are on the market at present which are used in intravenous replacement therapy. Some contain not only salts of sodium and potassium but also salts of calcium and magnesium. Vitamins are also added to intravenous fluids when their need seems to be apparent.

Whole blood and blood plasma are likewise given intravenously and are ideal to restore depleted blood volume.

d. **Intraspinal Injection.**—Various drugs may occasionally be injected into the subarachnoid space of the spinal cord. The term *intrathecal* also applies to this method of administration, although the latter term is less specific because the word “theca” (meaning sheath) also pertains to a tendon sheath. However, the terms *intraspinal*, *subarachnoid*, and *intrathecal* are used synonymously to mean the introduction of material into the cerebrospinal fluid.

Infection of the meninges is the great danger of intraspinal injection. A special technic is required and the procedure is done only by a doctor, with the assistance of a nurse.

Certain anesthetic agents are introduced this way, especially for operations below the diaphragm. Arsphenamine, tetanus antitoxin, and meningococcus antiserum are also given intraspinally.

To avoid increasing the cerebrospinal fluid an amount of fluid equal to, or slightly more than, the volume to be injected is withdrawn. When the drug to be injected is in a powder or crystalline form, it is usually dissolved in all or part of the cerebrospinal fluid that has been removed and then is reinjected into the subarachnoid space.

Care of Medicines

The care of the medicine closet and its contents is an important factor in promoting efficiency and preventing mistakes. The following precautions should be carefully observed:

1. All medicines should be kept in a special medicine closet.
2. The closet should always be locked, the key properly tagged and kept in a safe place to which only nurses and doctors have access.

The following abbreviations are commonly used in doctors' orders and prescriptions, and it is necessary for a nurse to know their meaning.

ABBREVIATION	Derivation	Meaning
āā	ana	(equal parts) of each
a.c.	ante cibum	before meals
ad	ad	to, up to
ad lib.	ad libitum	if desired
aq.	aqua	water
aq. dest.	aqua dest.	distilled water
b.i.d.	bis in die	two times a day
b.i.n.	bis in noctis	two times a night
c.	cum	with
caps.	capsula	capsule
comp.	compositus	compound
dil.	dilutus	dilute
elix.		elixir
ext.	extractum	extract
fld.	fluidus	fluid
Ft.	fiat	make
Gm.	gramme	gram
gr.	granum	grain
gtt.	gutta	a drop
h.	hora	hour
M.	misce	mix
m.	minimum	a minim
mist.	mistura	mixture
non rep.	non repetatur	not to be repeated
noct.	nocte	in the night
O.	octarius	pint
ol.	oleum	oil
o.d.	omni die	every day
o.h.	omni hora	every hour
o.m.	omni mane	every morning
o.n.	omni nocte	every night
os.	os	mouth
oz.	uncia	ounce
p.c.	post cibum	after meals
per	per	through or by
pil.	pilula	pill
p.r.n.	pro re nata	when required
q.h.	quaque hora	every hour
q. 2 h.		every two hours
q. 3 h.		every three hours
q. 4 h.		every four hours
q.i.d.	quatuor in die	four times a day
q.s.	quantum sufficit	as much as is required
R	recipe	take
s	sine	without
Sig. or S.	signa	write on label
Sol.		solution
s.o.s.	si opus sit	if necessary
sp.	spiritus	spirits
ss.	semis	a half
stat.	statim	immediately
syr.	sympus	syrup
t.i.d.	ter in die	three times a day
t.i.n.	ter in nocte	three times a night
tr. or tinct.	tinctura	tincture
ung.	unguentum	ointment
vin.	vini	wine

No nurse may alter or modify a doctor's order. If she has reason to think that a mistake has been made in the order, she should call the doctor's attention to it or report the situation to her immediate superior at once.

When a medication is ordered not to be repeated, it should be checked off immediately upon administration and the time of giving indicated. If such an order is not marked off, the drug may be given a second time to the detriment of the patient.

Prescriptions

Since a physician occasionally writes the orders which he expects the nurse to carry out, in the form of a prescription, it is essential that the nurse be able to read prescriptions.

A prescription is a written formula given by a physician to a pharmacist for the preparation of a medicine. It consists of four parts: the superscription which includes the name of the patient, the date and the symbol *R* meaning "take thou"; the inscription, which gives the names and amounts of the ingredients to be used; the subscription, giving the directions for the pharmacist; and the signature giving the directions to be written on the label.

The quantities of drug to be administered are written in either the Apothecaries' or the Metric System. English may be used.

Examples of Prescriptions.—

For Mr. James Brown	March 22, 1942.
<i>R</i>	
Antipyrinae	gr. xlv
Sodii bromidi	℥ ii
Codeinae phosphatis	gr. iv
Aq. dest. q s ad	℥ iv
M. et Sig. 3 i p c.	DR. STRONG
	Jan. 7, 1942.
For Mr. Wiley	
<i>R</i> ,	
Antipyrine	3.0
Sodium bromide	8.0
Codeine phosphate	0.3
Syr. of raspberry	60.0
Distilled water to	120
Mix and label: one teaspoonful every 4 hours	DR. TANNER.

The first prescription reads:

For Mr. James Brown—

Take thou of antipyrine 45 grains, of sodium bromide 2 drams, of codeine 4 grains, and add enough distilled water to make 4 ounces. Mix the ingredients and write on label: one teaspoonful after meals.

DATE March 25, 1942
 FOR Mr. John Doe-----ROOM--210 M.
 ADDRESS-12 Lake Street, Minneapolis, Minn.

R

Sulfathiazole gr. 7½
15 tablets

Sig: 7½ gr. t.i.d.

-----Dr. Smith-M D
 NEG 141 L. Jones - nurse

DATE March 25, 1942
 FOR Mrs. John Doe-----ROOM--215 S.
 ADDRESS-305 E. 4th Street, Chicago, Ill.

R

Aromatic Fluid Extract of Cascara
3iv

Sig: fl. 3 iv P.R.M.

-----Dr. Smith-M D
 NEG 141 J. King - nurse

Fig. 8.—The above samples represent forms of drug orders which may be sent to the hospital pharmacy. Nurses are frequently responsible for the copying of the drug order from the order book or the patient's order sheet and relaying the order to the pharmacist. Much can be done to prevent error and waste of time by making the order explicit and complete. The following points should be clearly indicated: 1. The date that the drug is ordered. 2. The room number of the patient. 3. The home address of the patient. 4. The full name of the drug; note that in 4 the exact preparation of cascara is indicated. 5. The amount of the drug. 6. The directions for taking the drug. 7. In case the drug is given other ways than by mouth, the method of administration should be mentioned. The pharmacist will send different preparations of a drug for parenteral and oral medication. 8. If the drug is a liquid and the solvent may be something other than water, the type of solution should be stated; e.g., aqueous solution, alcoholic solution, etc.

The nurse must get clearly in mind the distinction between the meanings of *s.o.s.* and *p.r.n.* *S.O.S.* refers to *one dose only*. More than one dose should not be given if a medicine is ordered *s.o.s.* *P.R.N.* means when required, or as often as necessary, and the nurse may use her own judgment about repeating the dose.

Suggestions for Giving Medicines Orally

To insure accurate results, when preparing or giving medicines, concentrate your whole attention upon what you are doing and do not permit conversation or other distractions to interfere with your work.

1. Read each medicine card carefully.
2. When calculating doses be sure your answer is correct. If in doubt, verify it.
3. If you think the maximum dose has been exceeded, always verify your suspicions.
4. Always read the label on the bottle three times: before taking the bottle from the shelf, before pouring the medicine, before returning the bottle to the shelf.
5. Never use medicines from an unmarked container and never leave medicine in a glass or bottle unmarked.
6. Always shake the bottle before pouring the medicine, especially if there is a precipitate.
7. When pouring fluids, hold the bottle with label upward to avoid soiling it. Use a piece of tissue to wipe mouth of soiled containers before replacing.
8. Measure the quantities as ordered, using the proper apparatus, graduated glasses for ounces or drams, minim glasses or minim pipettes for minims, medicine dropper for drops. Never give drops for minims or vice versa.
9. When measuring fluids, hold the graduate so that the line indicating the desired quantity is on a level with the eye. The quantity is read when the lowest part of the concave surface of the fluid is on this line.
10. Measure the exact amount ordered.
11. Never pour a medicine back into a bottle.
12. Do not handle tablets and pills with your fingers. Use the cap of the bottle or a clean medicine card to help get the tablet into the desired container.

18. Never allow one patient to administer medicines to another. Do not give medications prepared by another nurse. There is too much danger of making a mistake.

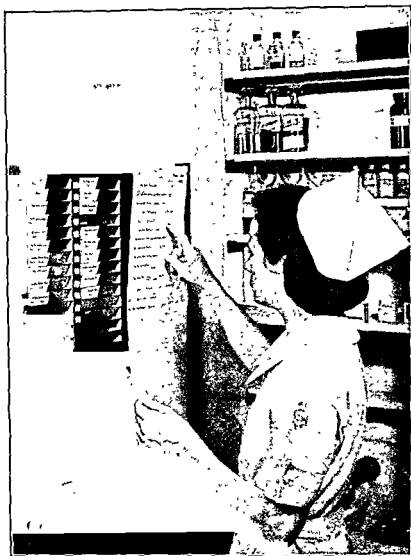


Fig. 10.—When a medicine list is used, the individual medicine cards should be checked with the medicine list to make certain that a discrepancy does not exist between the card and the list.

19. Never chart a medicine as given until the patient has actually swallowed it. If the patient fails to get the medicine, indicate the reason why it was omitted.
20. Give weak or helpless patients the assistance they need when giving them their medicine. Set the medicine tray down and use both hands in helping a very sick patient.

13. If medicines change color or form a precipitate when mixed, do not give them together without reporting this fact to the doctor. Such medicines are said to be *incompatible*, because of the chemical reaction which takes place between them.
14. Always recork bottles immediately after pouring medicine.
15. All orders for medication must be listed. The commonest method is to use cards of various colors, each color indicating a different time of administration. The orders, including the patient's name and medication, are transferred from the doctor's orders to the cards. The cards should be arranged in some systematic order. When the medications are to be given out, the nurse places the cards in a stack, and as the medication is prepared,

Name	Mr. John Doe
Room No.	120 M.
Sulfathiazole gr.15	
	10
	2
	6
F 45	

Name	Mrs. James King
Room No.	218 S.
Tincture of Belladonna	
M. 10	10
	2
	6

Fig. 9.—The type of medicine card which is used in many hospitals. The card is used for all medications. Re- indicate clearly (1) the full name of number, (2) the dosage, (4) the hour of medication. The color of the card is used to indicate the ward or ward.

attaches the card to the glass or container and does not remove it until the medicine is given to the patient. Call the patient by name before giving the medication.

16. Give all medications promptly and chart exact time of administration.
17. As a rule, the nurse should remain with the patient until the medication is taken. There is no other way of making certain that the patient really gets the medicine. If the nurse is to be held responsible for the patient receiving the medicine, she must make certain that the medication is swallowed.



Fig. 12—Weak patients or those who are very ill should be given special assistance in taking their medications.

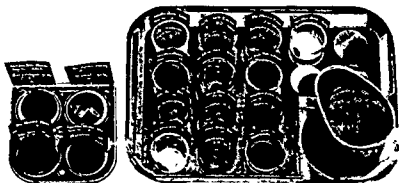


Fig. 13.—Two medicine trays with cards. The small tray at the left may be used for a number of patients, as in a double room or a small ward. Soufflé cups instead of medicine glasses may be used for capsules or tablets. The large tray is arranged for the administration of medications to a group of patients.

21. Irritating and distasteful drugs should be diluted and fresh water should be offered with the medications unless contraindicated, as may be the instances.
22. Medicine glasses after being used should be thoroughly washed in hot soapy water and then scalded with hot water. Glasses which were used for oily medications should be washed separately.
23. If the medicine tray is placed on a table in a patient's room while fresh water is obtained or something else is being done in the room, place the tray out of reach of the patient. Patients will pick up other patient's medicines and fumble with them. They have ample opportunity because they are curious to see what they have and what they are receiving.

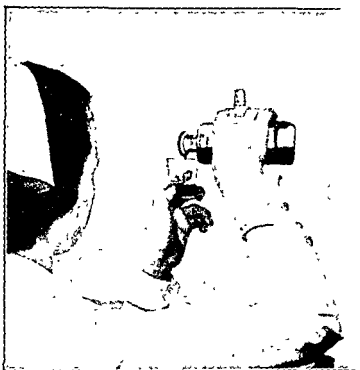


Fig. 11.—When pouring liquid medicine, the thumb is placed against the side of the medicine glass and the medicine is poured on a level with the top of the bottle so that the medication is not poured over the top.

The Psychologic Approach in Giving Medicines

How much the role of suggestion plays in drug therapy is not generally known but any observant nurse knows that it may make the difference between an outright refusal to take medicine and cooperation on the part of the patient.

6. How would you interpret the following:

Tr. Gentian Co. 3 i t.i.d., a.c.†

Nitroglycerin gr. $\frac{1}{100}$ Stat. and P.R.N.†

Milk of Magnesia 3 ss q. 4 h.†

Luminal gr. ss h.s.†

7. Explain the difference in meaning between the abbreviations s.o.s. and p.r.n.

8. Where is the physician's order book kept on your ward? List five or six drug orders which have been written within the past day or two. What was the nurse's responsibility for checking, signing, or posting of these orders? What happens to the order book when the pages are filled? In some hospitals, these books are kept for several years. Why?

9. Supposing that a patient is recovering from some form of gastric surgery and the amount of liquids that he is allowed to have at any one time is limited to 100 cc. The following orders are written for him during the course of a few days.

Mineral Oil and Milk of Magnesia

f3 ss aa b.i.d.

f3 ss aa t.i.d.

Prostigmine f3 ii t.i.d.

Creamalin tab. i t.i.d.

How would you distribute these medicines over the day so as not to exceed the fluid intake at one time and still allow for some water to be taken just after medications?

The nurse should go about the business of giving medicines with an air of assurance. The patient likes to feel that here is a nurse who knows what she is doing and why she is doing it. To be able to see her carefully check a medicine with the medicine card and hear her say, "This is your medication, Mr. Smith," helps to assure Mr. Smith that there is no doubt in the nurse's mind as to whom should be given this particular drug.

The medicine containers from which the patient is served his drug should be scrupulously clean, and the water supplied immediately after taking the medicine should be fresh and cold.

Orange slices, which may accompany a medicine tray containing glasses of mineral oil, can by the neat way they are arranged or the deftness with which they are handled, help to make the whole matter of taking the oil as pleasant as possible. Carelessly prepared medicines and lack of consideration in the way a medicine is handed to a patient can disgust him in the same way that poor food, cracked dishes, and inefficient service affect him in a restaurant.

There is little doubt that the efficacy of a medicine may be modified by the faith which the patient has in it and in the doctor who prescribed it. The nurse who dispenses the medicine may help to break or re-enforce the confidence which may have been painstakingly built up in the patient. She is never justified, however, in assuming anything but a cheerful optimism toward any patient's disease or his treatment.

Suggestions for Discussion and Study

1. If the calculation of a dose of medicine is your responsibility and you are not certain that your results are correct, what are you expected to do to verify your results before giving the dose to the patient?
2. If a patient has gone to another department of the hospital and one of his medications falls due while he is gone, what is your responsibility concerning—
 - a. the administration of that dose of medicine?
 - b. the charting concerning the medication?
3. What part does the nurse play on your hospital ward, in the preparation for giving a medicine?
 - a. intravenously?
 - b. intramuscularly?
4. List the advantages and disadvantages encountered in giving medicines by each of the methods mentioned in this chapter.
5. What are some of the habits which you are expected to learn in drug administration which promote safety for the patient and also for the nurse? Explain.

Drugs are used to produce the following local effects:

1. To treat infections (antiseptic)
2. To harden and contract the tissues (astringent)
3. To increase blood supply to part (stimulant)
4. To irritate tissues (irritant)
5. To destroy tissues (caustic)
6. To relieve pain (anodyne)
7. To produce anesthesia (local anesthetic)
8. To soothe (emollient)
9. To check bleeding (styptic)
10. To promote healing (vulneraries)
11. To coat and protect tissues (demulcent)
12. To produce counterirritation (counterirritants)
13. To destroy or expel intestinal worms (anthelmintic)
14. To supply a deficiency of secretion (acids)
15. To neutralize solutions in alimentary canal (acids and alkalies)

B. Systemic Action is the action of a drug on some tissue or organ remote from the site of application and occurs only after absorption, or the entrance of the drug into the blood stream. For example—morphine may be injected into the tissues of the arm but it is absorbed into the blood stream and carried to the brain where it exerts its chief action.

Effective systemic action is dependent upon the following:

1. The drug must be so administered that it will be introduced into the body, advantageously.
2. The drug must be absorbed. This presupposes solubility in one or more of the body fluids and ability to permeate cell membranes.
3. The drug must reach specific cells of the body so as to modify an already existing function.
4. The drug must be excreted. It may be eliminated unchanged or in combination with other waste products of the body, chiefly through the intestine, kidneys, lungs, and skin.

TYPES OF SYSTEMIC ACTION:

1. *Stimulation* is the action whereby the activity of a tissue is increased; e.g., caffeine increases the activity of the brain cells. Caffeine is therefore called a stimulant. It is of significance that prolonged overstimulation of cells will result in depression.

2. *Depression* is the action of a drug which results in decreased power of the cells to function. A drug which decreases the ability of the respiratory center to send out nerve impulses to the muscles of respiration would be called a respiratory depressant.

UNIT II

CHAPTER VII

THE ACTION OF DRUGS. DOSAGE

There are three general measures used in the treatment of a patient's complaint. The first, known as *symptomatic* therapeutics, deals only with the relief of symptoms without knowledge of the nature of the causative factors. Second *empirical* therapeutics deals with causative factors, using drugs whose physiologic action has been tested by experience and experimentation but whose mechanism of action is imperfectly understood. Lastly, *rational* therapeutics, which is the scientific treatment of a disease, the action of the drug on the tissues being understood. An example of rational therapeutics is the use of quinine in the treatment of malaria—it relieves the symptoms because it kills the plasmodium that causes the disease.

Many drugs are of great value in the treatment of disease. The purpose of any therapeutic measure may be stated as follows:

1. To remove or destroy the causative agent.
2. To relieve the symptoms.
3. To restore normal metabolism.
4. To restore the organism to that state called "normal health" in which anabolism and catabolism are proportional to the metabolic requirements of the organism.

It is important to bear in mind that these requirements are not the same in all patients but vary considerably with each individual.

ACTION OF DRUGS

Most drugs in themselves do not cure a disease but materially aid that power which we know as "nature" to complete the process. In other words, no drug can make a tissue perform functions for which it is not physiologically adapted. It may cause tissues to perform their usual activities more or less swiftly, intensely, or efficiently, but it will not produce new miracles.

A. Local Action is the effect produced by a drug at the point of application on the skin or mucous membrane; e.g., the application of tincture of iodine to a small abrasion or the application of cold cream to the skin of the face.

8. *Antagonistic Action*.—Two or more drugs which have an opposite effect on an organ are said to be antagonistic. They are valuable in counteracting one another in case of poisoning. Pilocarpine may be counteracted by atropine, and strychnine by an anesthetic or a sedative.

9. *Cumulative Action*.—Some drugs are excreted so slowly that the whole of one dose is not eliminated before the next dose is given. In this way the drug accumulates in the body and if administration is prolonged, toxic symptoms may appear. Drugs such as mercury, the iodides, and digitalis have a cumulative action.

10. *Synergistic Action*.—Drugs which have a similar effect on an organ may be additive or synergistic. When two or more synergistic drugs are administered together, each aids the effect of the other and the combined effect or synergistic action is often greater and more satisfactory than if one is given in relatively greater proportion. Caffeine and acetanilid are used together in headache powders, and cathartic drugs in various combinations because of their synergistic action. An additive effect is the effect obtained by the additive action of one-half dose of one drug with one-half dose of a similarly acting drug. If the effect is the same as a full dose of either drug, the action is additive. If the effect is greater than a full dose of either drug, their action is synergistic.

11. *Idiosyncrasy* is any unusual response to a drug. It may manifest itself by (1) over response or abnormal susceptibility; (2) under response showing abnormal tolerance; (3) different effect than usual, such as excitement or delirium after morphine; (4) abnormal symptoms which are unexplainable.

12. *Tolerance* is an acquired reaction to a drug in which the dose must be progressively increased in order to maintain a given therapeutic response. Drugs to which people commonly develop a tolerance are tobacco, morphine, and alcohol.

13. *Habituation* is a condition which is characterized by psychic craving for a drug when it is withdrawn. When the psychic influence is strong, people may become habituated to almost anything.

14. *Addiction* is a state in which altered physiological processes result from the withdrawal of a drug, as well as a psychic craving. The drug has become essential to the maintenance of ordinary cellular activities. Morphine is a well-known drug to which people become addicted and suffer a variety of withdrawal symptoms when the drug is denied them.

Drugs may produce stimulation or depression of vital processes in a number of ways. In many instances the exact site of action is not known.

- a. The site of action may be remote from the tissue which responds; e.g., blood pressure may be lowered by action on the vasomotor center of the brain. Changes in respiration may be due to action on the carotid sinus rather than on the respiratory center.
- b. Direct action on the effector cells, either the surface or the interior of the cell.
- c. Some drugs appear to exert their action by preventing or promoting the action of some other drug. This is sometimes accomplished by inhibiting enzyme action, or by acting upon glands which furnish the chemical regulators.

3. *Irritation* is an action which produces slight temporary damage to tissues. Castor oil causes slight damage to the mucous membrane of the intestine and is known as a chemical irritant. Mild irritation usually results in stimulation of cells while prolonged irritation causes depression of cellular activity, and marked irritation may cause inflammation and death of tissue. The mercuric diuretics in small doses may cause increased flow of urine because of their mild irritation, but if the use of these drugs is prolonged the kidneys may become inflamed and suppression of urine results.

4. *Physiologic Action* is the action of a drug on normal healthy tissues.

5. *Therapeutic Action* is the action of a drug on diseased tissues or in the sick individual. The action of a drug in a well person and in a sick individual may be quite different. Thyroid extract may relieve the symptoms of hypothyroidism in the patient with myxedema and make him well, but this same drug in the normal individual may result in symptoms of hyperthyroidism.

6. *Side Action* is the action of a drug other than the one for which it is given. The therapeutic action of a drug used for one condition may become a side action when the drug is administered for a different purpose. Morphine sulfate is commonly ordered for its analgesic effect and not for its ability to cause constriction of the pupil. The latter effect would result from a side action.

7. *Untoward Action*.—When a side action is more or less harmful, it is known as an untoward action. The action of morphine which results in nausea and vomiting and in habit formation is undesirable and harmful frequently. This action is then said to be untoward.

4. The restoration of normal physiologic function by the replacement of essential biological substances; for example, the use of cortical hormone in the treatment of patients with Addison's disease or the use of thyroid extract for patients with hypothyroidism.

DOSAGE OF DRUGS

Posology (Gr. *posos*, how much + *logy*, discourse) is the study of doses.

Dose—the amount of drug which is given for a therapeutic effect.

Minimal dose—the smallest amount of a drug which can accomplish a therapeutic effect.

Maximal dose—the largest amount of a drug which will produce a therapeutic effect without accompanying symptoms of toxicity. To produce the desired effect, many drugs must be given to the limit of the patient's tolerance.

Toxic dose—the amount of a drug which will cause untoward effects.

Lethal dose—the amount of drug which will cause death.

The responsibility of dosage rests on the physician, but the nurse should know dosage and be on the alert to detect errors. She may not change prescribed dosage of her own accord, but if there is an apparent error, she is responsible for consulting with the proper authority in order to have the dosage verified.

M.L.D. = 50% Mortality

Conditions Modifying Dosage

The dose of a drug is based on the age, weight, condition, and individuality of the patient. Factors influencing dosage, the climate, the nature of the disease, weight, sex, temperament, and physical condition of the individual, all have a modifying influence. Some people are poisoned by drugs that are ordinarily safe. Often, however, the patient knows that he is very susceptible to some drug and will tell the nurse or doctor.

The frequency of dosage is determined by the time of absorption, duration of action, and rate of elimination of the drug. Some drugs act quickly and are eliminated or detoxified rapidly, others tend to cumulate in the body.

A few of the rapidly acting drugs are:

Alcohol	Ether
Ammonia	Salicylates
Camphor	Strophantin (intravenously)
Chloral	Strychnine

Additional Ways in Which Systemic Action May Be Described

Selective Action.—Most drugs do not affect all the organs or tissues of the body but show a selective ability which makes them act only upon certain types of cells. Thus strychnine acts chiefly on the cells of the spinal cord, morphine upon the brain. This property is called selective action. It is probably due to the fact that certain cells contain some chemical substance for which the drug has a marked affinity.

General Action.—Drugs which have little or no selective action but which appear to affect all protoplasm are said to have a general action. A few drugs, such as alcohol, chloral hydrate, and quinine, are said to have a general action. Included in this group are also most of the antiseptics, acids, alkalies, and heavy metals.

How Drugs Produce Their Effects

Drugs owe their efficiency to the way in which they react with the cells of the tissues with which they come in contact.

1. The reaction may be chemical, in which case the molecules or ions of the drugs in solution form combinations with the albumin or other constituents of the cell, the exact nature of which is unknown, or by their mere presence change the environment of the cell so that its activity is modified.

2. The reaction may be physical, as when some of the cell constituents are temporarily dissolved in the drug, to be restored to normal condition again when the drug is eliminated.

3. Many physical changes are due to osmotic pressure changes which alter the water content of the cell.

Osmosis, or the action due to osmotic pressure, is commonly called "salt action" in connection with drugs because it is so pronounced in the case of certain medicinal salts, but it occurs with all substances in solution. According to the law of osmosis, if two solutions of different concentration are separated by an animal membrane, they tend to equalize in concentration. The cell walls are animal membranes. If the concentration of the drug which comes into contact with them is greater than that of the fluid content of the cell, the former draws water from the cell, shrinking it and itself becoming more dilute. If the solution of drug is weaker, it gives up water to the cell, which in turn swells until the pressure within and without its walls is equal. The general effect of salt action is to change the watery content of the cell, and thereby alter the concentration of their soluble constituents. These changes alone are often all that is required to produce the desired therapeutic effect.

4. The restoration of normal physiologic function by the replacement of essential biological substances; for example, the use of cortical hormone in the treatment of patients with Addison's disease or the use of thyroid extract for patients with hypothyroidism.

DOSAGE OF DRUGS

Posology (Gr. *posos*, how much + *logy*, discourse) is the study of doses.

Dose—the amount of drug which is given for a therapeutic effect.

Minimal dose—the smallest amount of a drug which can accomplish a therapeutic effect.

Maximal dose—the largest amount of a drug which will produce a therapeutic effect without accompanying symptoms of toxicity. To produce the desired effect, many drugs must be given to the limit of the patient's tolerance.

Toxic dose—the amount of a drug which will cause untoward effects.

Lethal dose—the amount of drug which will cause death.

The responsibility of dosage rests on the physician, but the nurse should know dosage and be on the alert to detect errors. She may not change prescribed dosage of her own accord, but if there is an apparent error, she is responsible for consulting with the proper authority in order to have the dosage verified.

M. L. D. = 50% Mortality

Conditions Modifying Dosage

The dose of a drug is based on the age, weight, condition, and individuality of the patient. Factors influencing dosage, the climate, the nature of the disease, weight, sex, temperament, and physical condition of the individual, all have a modifying influence. Some people are poisoned by drugs that are ordinarily safe. Often, however, the patient knows that he is very susceptible to some drug and will tell the nurse or doctor.

The frequency of dosage is determined by the time of absorption, duration of action, and rate of elimination of the drug. Some drugs act quickly and are eliminated or detoxified rapidly, others tend to cumulate in the body.

A few of the rapidly acting drugs are:

Alcohol	Ether
Ammonia	Salicylates
Camphor	Strophantin (intravenously)
Chloral	Strychnine

Additional Ways in Which Systemic Action May Be Described

Selective Action.—Most drugs do not affect all the organs or tissues of the body but show a selective ability which makes them act only upon certain types of cells. Thus strychnine acts chiefly on the cells of the spinal cord, morphine upon the brain. This property is called selective action. It is probably due to the fact that certain cells contain some chemical substance for which the drug has a marked affinity.

General Action.—Drugs which have little or no selective action but which appear to affect all protoplasm are said to have a general action. A few drugs, such as alcohol, chloral hydrate, and quinine, are said to have a general action. Included in this group are also most of the antiseptics, acids, alkalies, and heavy metals.

How Drugs Produce Their Effects

Drugs owe their efficiency to the way in which they react with the cells of the tissues with which they come in contact.

1. The reaction may be chemical, in which case the molecules or ions of the drugs in solution form combinations with the albumin or other constituents of the cell, the exact nature of which is unknown, or by their mere presence change the environment of the cell so that its activity is modified.

2. The reaction may be physical, as when some of the cell constituents are temporarily dissolved in the drug, to be restored to normal condition again when the drug is eliminated.

3. Many physical changes are due to osmotic pressure changes which alter the water content of the cell.

Osmosis, or the action due to osmotic pressure, is commonly called "salt action" in connection with drugs because it is so pronounced in the case of certain medicinal salts, but it occurs with all substances in solution. According to the law of osmosis, if two solutions of different concentration are separated by an animal membrane, they tend to equalize in concentration. The cell walls are animal membranes. If the concentration of the drug which comes into contact with them is greater than that of the fluid content of the cell, the former draws water from the cell, shrinking it and itself becoming more dilute. If the solution of drug is weaker, it gives up water to the cell, which in turn swells until the pressure within and without its walls is equal. The general effect of salt action is to change the watery content of the cell, and thereby alter the concentration of their soluble constituents. These changes alone are often all that is required to produce the desired therapeutic effect.

It is difficult to give definite dosage in relation to weight in obese persons, but the average weight will enable one to determine this rather satisfactorily. More than 10 per cent above or below the average weight may be considered overweight or underweight. If overweight the dose should be lower because of fat; if underweight it may be lower, because of less active tissue.

Temperament.—Nervous persons require smaller doses of stimulants and larger doses of depressants than average persons. Phlegmatic persons require larger doses of stimulants and smaller doses of depressants.

Method of Administration.—The dose of a drug depends on the method of administration. This is due to the rate at which it enters the circulation.

1. The oral method requires the usual dose.
2. Subcutaneous injection requires $\frac{1}{2}$ the oral dose.
3. Intramuscular injection requires about $\frac{1}{3}$ the oral dose.
4. Intravenous injection requires about $\frac{1}{4}$ the oral dose or less.
5. Rectal administration requires about twice the oral dose.

Time of Administration.—This refers particularly to oral administration of drugs in relation to meals. Absorption is delayed by the presence of food in the stomach and intestine and proceeds more rapidly when these organs are comparatively empty, thus modifying the dose necessary for effect. It is readily noticed that the amount of a medicine to relieve a headache needs to be greater if it is taken after a meal than if taken before a meal. Large doses of irritating drugs, however, are more easily tolerated if there is food in the stomach.

Absorption and Excretion.—Doses are often given every three or four hours. This is due to the fact that many drugs are excreted in this time. If drugs are slowly excreted or tend to accumulate in the body, the dose must be given less frequently. Iodides tend to accumulate, as does digitalis. Salicylates are rapidly excreted.

Condition of the Patient.—Intense pain may call for larger doses of morphine than the average. Larger amounts of insulin are indicated in cases of diabetes complicated by fever or infection. Severe cardiac decompensation may call for very large doses of digitalis for rapid effects.

Dosage in Relation to Types of Pharmaceutic Preparations

There are very few rules in dosage. A knowledge of doses is gained mainly by experience in using drugs, and no one should rely on his memory until much experience has made it certain.

These act in from a few minutes to an hour, hence the time of administration is from every hour to every three or four hours according to need.

Some of the more slowly acting drugs are:

Arsenic	Quinine
Atropine	Some of the synthetic antipyretics
Bromides	Some of the synthetic hypnotics
Digitalis	Thyroid preparations

Age is of importance in the calculation of dosage. Children have more central nervous system for their weight than adults; and are therefore more susceptible to drugs which act on the nervous system. Young tissues tend to be more sensitive to all forms of drugs than are those of the adult. Individuals of advanced years are also more susceptible to drugs, probably due to changes in weight.

Weight.—Drugs act primarily on the active tissues of the body. This means muscle tissue, nerve tissue, and epithelium. Fat, since it is an inactive tissue, must be discounted to a great extent when computing the weight of the body for the calculation of dosage. While fat per se is practically dead tissue, it can however act like a sponge and hold drugs on the living protoplasm.

A large strong child should get more than a weakling of the same age. Also a small adult should get less than a large robust individual. The blood of an average adult individual is about $\frac{1}{13}$ the weight of the body. This is not true of children or obese persons. The obese, therefore, may require less than a normal adult, because the volume of blood is in relation to the active tissue and to the nervous system.

AVERAGE WEIGHT TO HEIGHT AT DIFFERENT AGES

FT. IN.	YEAR							
	15-24	25-29	30-34	35-39	40-44	45-49	50-54	55-60
5-0	120	125	128	131	133	134	134	134
5-1	122	126	129	131	134	136	136	136
5-2	124	128	131	133	136	138	138	138
5-3	127	131	134	136	139	141	141	141
5-4	131	135	138	140	143	144	145	145
5-5	134	138	141	143	146	147	149	149
5-6	138	142	145	147	150	151	153	153
5-7	142	147	150	152	155	156	158	158
5-8	146	151	154	157	160	161	163	163
5-9	150	155	159	162	165	166	167	168
5-10	154	159	164	167	170	171	172	173
5-11	159	164	169	173	175	177	177	178
6-0	165	170	175	179	180	183	182	183
6-1	170	177	181	185	186	189	188	189
6-2	176	184	188	192	194	196	194	194
6-3	181	190	195	200	206	204	201	198

It is difficult to give definite dosage in relation to weight in obese persons, but the average weight will enable one to determine this rather satisfactorily. More than 10 per cent above or below the average weight may be considered overweight or underweight. If overweight the dose should be lower because of fat; if underweight it may be lower, because of less active tissue.

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Dosage in Relation to Types of Pharmaceutic Preparations

There are very few rules in dosage. A knowledge of doses is gained mainly by experience in using drugs, and no one should rely on his memory until much experience has made it certain.

The following may be an aid:

Infusions	Dose		
with the exception	3ii-iv	=	60-120 cc.
of digitalis	3iss	=	6 cc.
Emulsions	3ss-iv	=	2-15 cc.
Tinctures			
Potent	m x	=	0.6 cc.
Nonpotent	3ss-j	=	2-4 cc.
Fluidextracts			
Potent	m j	=	0.06 cc.
Nonpotent	m xv-xxx	=	1-2 cc.
Extracts			
Potent	gr. ¼	=	0.015 Gm.
Nonpotent	gr. ij-iv	=	0.1-0.25 Gm.

Suggestions for Study and Review

- What is meant by the local action of drugs? State several local effects which drugs produce.
- What are the aims of therapeutic action in the treatment of disease?
- What are four factors upon which effective therapeutic action of drugs depends?
Fill in the following blanks with the name given to the type of systemic drug action represented.
- Histamine is a substance which is sometimes given to relieve certain types of symptoms although the way in which it affects the tissues has not been thoroughly substantiated by laboratory experimentation.

- An opiate decreases the activity of many of the nerve cells.

- Caffeine increases the activity of cells in the brain.

- Thyroid extract when given to a patient with hypothyroidism, relieves many or all of the patient's symptoms.

- Thyroid extract when administered to a normal individual is very likely to produce symptoms of hyperthyroidism.

- Castor oil acts upon the entire intestine by producing a slight irritation to the lining tissues.

- When morphine is given to a patient following surgery, it is very likely given to relieve pain but it may in a susceptible individual cause nausea and vomiting, and it will also cause some constriction of the pupil of the eye.
 - The action of morphine whereby pain is relieved is

 - The action whereby nausea and vomiting is produced is *depression of the vomiting center*
 - The action resulting in a smaller pupil is

 - The ability of morphine to act primarily on nerve tissue illustrates

e. If the ordinary dose of morphine had no effect or had produced restlessness and excitement, the reaction would be known as

f. Morphine is sometimes given along with magnesium sulfate to produce a longer or more satisfactory effect. This type of action is called

11. Atropine brings about decreased activity of effector cells connected with the parasympathetic nervous system, while eserine brings about increased activity of the same effector cells.

Antagonism

12. Mrs. Smith has taken cathartics for a long time. She found that it was necessary to increase the dosage from time to time to get the same effect. This type of action is called

Tolerance

13. What is meant by a dose of medicine? Define minimal, maximal, and lethal dose. Enumerate several factors which are considered when dosage is determined for patients.

14. In what respects may a nurse give more intelligent nursing care if she has some knowledge of the dosage of drugs? Be specific.

CHAPTER VIII

COMMON POISONS AND ANTIDOTES

Toxicology is the study of the action of, detection of, and antidotes for, poisons. *

1. **Definition of a Poison.**—A poison may be defined as any substance which when applied to the body or introduced into the system, in relatively small amounts in whatever manner, causes death or serious bodily harm.

2. **General Symptoms of Poisoning.**—One may suspect a poison has been taken when sudden violent symptoms occur, such as vomiting, collapse or convulsions. When poisoning is suspected, the nurse should send for the physician, and in the meantime find out if possible what poison has been taken and how much, and then apply suitable first-aid antidotes.

3. **Avenue of Entry.**—Poisons may enter by the mouth or may be absorbed by the skin in amounts sufficient to cause death or severe toxic symptoms, as from lotions or salves containing opium, corrosive sublimate, arsenic, etc. Gaseous or volatile poisons may enter the lungs through inspired air; e.g., illuminating gas, carbon monoxide, or chlorine. Poisons may gain access to the circulation through ulcerated surfaces or wounds; by direct injection into the tissues as by hypodermic injection, poisoned weapons or snake bites; or they may be introduced by way of the mucous membrane of the rectum, urethra, or vagina.

4. **Range of Susceptibility to Poisoning.**—Most medicinal agents are poisonous if taken in sufficient quantity, this quantity varying with the individual, the state of health, fullness or emptiness of the stomach, habit, and other circumstances. The influence of habit is shown by opium habitués who take enormous doses of drug without immediate evil effects. A special susceptibility to certain substances, called idiosyncrasy, is noted in some individuals. Races and individuals may possess or attain a high degree of immunity to particular poisons—the Oriental is much less susceptible to opium than the European, and the latter bears alcohol better than savage races. In certain diseases there is a diminished susceptibility to the action of particular poisons, while in others there is increased sensibility. Thus, in tetanus, hydrophobia, mania or delirium tremens, doses of

various sedatives may be given with benefit which would in health prove fatal; on the other hand, when there is a predisposition to apoplexy, an ordinary dose of opium may cause death. Some poisons are harmless to the stomach, but violently toxic when injected beneath the skin.

5. Classification of Poisons.—Poisons are best classified according to their physiologic action upon the system when it is in a healthy condition.

A. Corrosives are poisons whose action is chiefly local and whose effects are characterized by tissue disintegration. The strong acids and bases are the chief corrosive poisons.

Mineral acids—sulfuric, nitric, and hydrochloric acids.

Caustic alkalies—potassium hydroxide, sodium hydroxide.

Calcium oxide (quicklime).

Phenol.

B. Irritants are poisons which produce very mild destruction of tissue or irritation. They are chiefly inorganic substances. Bichloride of mercury and the arsenicals are good examples. Some poisons are capable of producing both irritant and corrosive effects.

C. Neurotoxins are poisons whose chief effect is on the nervous system. They are mostly of vegetable origin. The various alkaloids such as morphine, atropine, and strychnine as well as the glucosides such as digitalin and strophanthin are neurotoxic poisons.

6. Symptoms.—

A. Corrosive poisons act locally either on the surface of the body, causing deep and painful destruction of tissues, or internally, producing intense burning pain in the mouth, throat, and stomach. There is intense nausea, vomiting, and purging, and the vomitus or purged material often contains shreds of mucous membrane and blood. In case of acid burns, the lips become dry, shrunk, and white or yellow in color. In alkali poisoning, the mouth and lips are swollen and a white crust forms. In phenol poisoning there is an odor of phenol on the breath, and the urine becomes a characteristic dark green color.

In most cases of corrosive poisoning the patient goes into shock, the skin becomes cold and clammy, the pulse becomes feeble and irregular, and death is frequently caused by hemorrhage or perforation of the stomach or intestine. In case a corrosive poison is inhaled, edema of the glottis further complicates matters. The patient usually retains consciousness until the end.

B. *Irritants* produce symptoms characteristic of irritation; nausea and vomiting, diarrhea, and pain in the abdomen. Shreds of epithelium and blood are usually absent from the vomitus and purged material. Death is usually due to remote changes in organs like the liver and kidney.

C. *Neurotropic poisons* must be studied separately because there are separate symptoms which characterize each one, and they will be presented in later chapters where these drugs are discussed. Nerve poisons as a rule produce little or no tissue destruction. However, drowsiness, dizziness, headache, delirium, stupor, coma, and convulsions are symptoms associated with poisons which affect the nervous system.

7. **First Aid Treatment of Poisoning.**—Poisoning may be suspected when alarming symptoms such as those enumerated above develop suddenly. The duty of the nurse is to send at once for a physician and, pending his arrival, to ascertain if possible the cause of the symptoms and to apply suitable first aid measures. Further treatment of the case is the responsibility of the physician.

A few general principles of first aid treatment of poisoning may be given. They are:

A. When a poison has been taken by mouth, *the stomach should be emptied immediately* by means of the stomach tube or emetics, except where there is severe corrosion and perforation of the stomach is feared. No force should be used in inserting the stomach tube, and false teeth, if present, should be removed prior to the passage of the tube.

Emetics.—

- a. Peripheral: Finger to the throat, quantities of tepid water, or tepid water with mustard (one teaspoon to a glass), warm milk in large quantities, common salt solution, or weak soap-suds. These often act with great promptness.
- b. Central: Apomorphine hydrochloride, gr. $\frac{1}{10}$. This drug tends to be depressing and is not popular because of this action.

In addition zinc sulfate (gr. 15 in half a glass of water, or copper sulfate, gr. 4 in warm water, may be given. Ipecac in the form of syrup is found in many households and may be given in doses of one or two tablespoonfuls to adults or half that amount to children. It is safe and nonirritating, but is too slow for emergencies. In poisoning, it is better to use almost any emetic at once than to lose valuable time getting the right one.

B. After the stomach has been emptied, it is necessary to administer the proper antidote. An *antidote* is any agent used to counteract the action of a poison. There are three kinds of antidotes: (1) physical or mechanical, (2) chemical, and (3) physiologic.

A *physical antidote* is one that envelops or mixes with the poison and prevents its absorption, soothes, and protects the tissues, and may aid in removal of the poison.

Demulcents, emollients, emetics, cathartics, and the stomach tube are used as physical antidotes.

Milk, white of egg, boiled starch or porridge, gruels, barley water, mashed potato, mucilage of acacia, are suitable demulcents. Fixed oils like olive, cottonseed, cod-liver, or liquid petrolatum may be used, but in cases where the poison is soluble in the oil, like cantharides or phosphorus, the stomach should be emptied after giving the oil.

A *chemical antidote* is one that reacts with the poison and neutralizes it. Common salt is an excellent antidote for silver nitrate. The products formed, silver chloride and sodium nitrate, are both harmless. Magnesium oxide, milk of magnesia, or baking soda are chemical antidotes for acids. In general, it is to be remembered that alkalies counteract acids and vice versa. *Care should be used when sodium bicarbonate is given because if too much gas is given off in the reaction, the pressure may rupture the corroded stomach.* For this reason, milk of magnesia or calcium carbonate may be preferable. Poisoning with irritant metallic salts is best treated with albumin in the form of white of egg, an insoluble albuminate being formed. The antidote for the vegetable alkaloids such as morphine, atropine, or strychnine is tannic acid or potassium permanganate. Both the tannic acid and the potassium permanganate (1:2000) may be used to wash out the patient's stomach. The tannic acid may be conveniently obtained from strong green tea and it brings about precipitation of the alkaloids while the potassium permanganate brings about oxidation of the alkaloids.

Chemical antidotes act only on such portions of the poison as have not been absorbed, and must be given promptly. As a rule an emetic is given after a chemical antidote, or the stomach pump may be used with care to avoid perforation.

A *physiologic antidote* is one that produces the opposite systemic effect from that of the poison. If a person has taken or been given too much pilocarpine the sweating is readily counteracted by the hypodermic use of atropine ($\frac{1}{60}$ to $\frac{1}{30}$ grain). Caffeine is the physi-

ologic antidote for morphine and sedatives like pentobarbital or an anesthetic for strychnine poisoning. If there are spasms, use ether first, a sedative later.

Artificial respiration, where indicated, and heat also are physiologic antidotes.

C. Promote Elimination.—This may be accomplished by the use of certain cathartics like salines, croton oil or castor oil or by irrigations. Diuretics may promote excretion from the kidney and diaphoretics may promote skin excretory function.

D. Sustain the Patient. In an effort to locate the exact antidote for a poison the most fundamental treatment may be overlooked, important though the antidote may be. The patient should be kept warm and quiet unless the poison is a depressant. Mitigate the pain as much as possible. Exclude friends and relatives with the exception of one or two of the most cooperative members. Sometimes stimulants will be indicated.

Treatment for Specific Poisons

Mineral Acids, Sulfuric Acid:

1. Do not use stomach tube or emetic for fear of perforating stomach
2. Neutralize the acid by giving one of the following alkalies:
 - (a) Magnesium oxide, several tablespoonfuls in water
 - (b) Milk of magnesia
 - (c) Aromatic spirit of ammonia, a tablespoonful in a glass of water
 - (d) Washing soda
 - (e) Chalk solution of soap
 - (f) Plaster scraped from wall
3. Give one of the following demulcents:
 - (a) White of egg
 - (c) Flour and water
 - (b) Milk
 - (d) Liquid petrolatum
4. Treat collapse with heart stimulants: caffeine, atropine, coramine, etc. Keep the patient warm
5. Give analgesics for pain

Caustic Alkalies; Quicklime:

1. Do not use stomach tube or emetics
2. Neutralize the alkali by giving one of the following acids freely:
 - (a) Dilute vinegar
 - (b) Lemon juice
 - (c) Acetic acid, 5 per cent

3. Give albumen (white of egg, or the whole egg), olive oil, butter, or milk as demulcents
4. Administer heart stimulants

Phenol:

1. The main objective in the treatment of phenol poisoning is to remove the poison from the stomach as quickly as possible to prevent extensive absorption. The lavage fluid should be something that will dissolve the phenol and retard absorption. Olive oil has been found to be effective. Alcohol should be avoided because it favors gastric absorption. After lavage some fresh olive oil may be left in the stomach for its demulcent effect
2. Keep the patient warm; treat for shock
3. Give isotonic salt solution intravenously to promote diuresis and to protect the kidney
4. If phenol has been applied to the skin or mucous membranes, it may be removed with 50 per cent alcohol
The toxic dose of phenol is from 8 to 15 grams (adults)

Bichloride of Mercury or Corrosive Sublimate:

1. Empty stomach with stomach tube or emetic
2. Give whites of one dozen eggs
3. Give tannic acid, strong tea or coffee
4. Administer morphine sulfate
5. Administer stimulants
6. Keep patient warm

The true irritant poisons most commonly used include besides certain of the corrosive poisons already mentioned, the salts of the metals, arsenic, copper, lead, silver, and zinc; and phosphorus and iodine. In concentrated form, most of them cause irritation of the gastrointestinal tract and also show specific action on various organs after their absorption into the blood stream.

The treatment of irritant poisoning is as follows:

1. Use the stomach tube or give an emetic
2. Give as demulcents milk, raw eggs, or egg white
3. Give tannic acid or strong tea to combine with the metals and neutralize them
4. Treat shock with heart stimulants
5. Give chemical antidote

<i>Poison</i>	<i>Antidote</i>
Arsenic	Arsenic antidote (dialyzed iron)
Lead	Magnesium sulfate
Silver Nitrate	Sodium chloride (salt)
Zinc	Sodium or potassium carbonate
Phosphorus	Potassium permanganate, copper sulfate or liquid petrolatum
Iodine	Starch

POISONOUS FOODS

Many foods, owing either to their inherent properties (mushrooms and other fungi) or to the development of putrefactive bodies from them (ptomaines), produce symptoms of poisoning when eaten. The symptoms are very diverse, but intense gastrointestinal irritation is common to all of them and they may therefore be appropriately classed as irritants. Mushroom poisoning arises through mistaking various fungi, such as mushrooms, toadstools, and truffles, for edible varieties. The toxin in many of these substances is muscarine, a deadly alkaloidal poison, producing violent vomiting, colic, thirst, dyspnea, paralysis, and death. Ptomaine poisoning is due to the products of putrefactive decomposition in animal or vegetable matter. The ptomaines are alkaloids and resemble chemically many of the vegetable alkaloids. Not all ptomaines are poisonous and not all food poisons are ptomaines. The foods which sometimes produce symptoms of poisoning, whether ptomaine or other poisons, are corned beef, sausage, pickled or decaying fish, putrid game, cheese, milk, shellfish, particularly mussels and crayfish, etc. The treatment of food poisoning from whatever cause is prompt evacuation of the stomach, preferably by stomach tube, using plenty of water, and administration of tannic acid or strong tea; a large dose of Epsom salts or milk of magnesia to empty the bowels and to prevent absorption. Morphine may be given to counteract the abdominal pain, and stimulants are indicated if there is prostration.

Suggestions for Study and Review

1. Why must the amount of a substance be considered before it can be called a poison? Could excess amounts of water in the tissues act as a poison? Would water ever be considered a poison?
2. What are factors which might modify the action of a poison?
3. What is an antidote? How are antidotes classified?
4. How are poisons classified?

5. Describe the relationship between the type of poison and the corresponding symptoms you would expect.
6. Name several common household emetics. What is the disadvantage in the use of apomorphine as an emetic?
7. What natural excretory channels could be stimulated whereby elimination of the poison would be hastened?
8. What supportive measures might you seek to provide for the patient who shows symptoms of shock and who is surrounded by anxious relatives or friends?
9. You have reason to think that a person has been poisoned; how would you set about making a thorough inspection of the patient and his immediate environs in order to give an intelligent report to the physician?
10. Mention a specific antidote which could safely be used for each of the following and explain why it is a good antidote.
 - a. Lye -----
 - b. Hydrochloric acid -----
 - c. Bichloride of mercury -----
 - d. Iodine -----
 - e. Phenol -----
11. Name the antidotes used in poisoning by the salts of the following:
 - a. Arsenic
 - b. Lead
 - c. Silver
 - d. Zinc
12. What is the antidote used in poisoning by:
 - a. Phosphorus
 - b. Iodine
13. What are the commonest forms of food poisoning?
14. What is the treatment of food poisoning?

CHAPTER IX

COMMON ACTIVE PRINCIPLES OF PLANT DRUGS

The therapeutic effects produced by any drug of vegetable origin are due to chemical substances which they contain. These substances are called *active principles*. They can usually be extracted from the plant by decomposition and produce effects which are similar to, but more potent and reliable than, those of the crude drug. Most of the active principles belong to the following groups of chemical substances:

Acids	Oils
Alkaloids	Resins
Carbohydrates	Oleoresins
Gums	Balsams
Glucosides	Tannins
Saponins	Enzymes
Neutral Principles	Hormones

1. Plant Acids

Plant acids occur chiefly in fruits and are the substances which give them their sour taste. The most common one, citric acid, occurs in the juice of lemons, oranges, limes, grapefruit, gooseberries, and other acid fruit and berries. Tartaric acid is found in many fruits, chiefly in grapes, and is made from crude cream of tartar which deposits on the side walls of wine vats during the fermentation of grape juice. Acetic acid occurs in vinegar. Concentrated acetic acid or glacial acetic acid contains 99 per cent of acetic acid and is caustic in action. Plant acids have many of the same properties as inorganic acids but ionize only slightly in aqueous solutions. They all contain the group—COOH.

2. Alkaloids

Alkaloids (literally, alkali-like) are as a rule the most important medicinal principles of the plants from which they are derived and in moderate doses constitute therapeutic agents of highest value. In larger quantities, however, they are extremely poisonous. Most alkaloids are, chemically, compounds of carbon, hydrogen, nitrogen, and oxygen. They are nonvolatile solids and can mostly be obtained

in the form of colorless crystals. A few, like nicotine and coniine, do not contain oxygen. Those that do not contain oxygen are liquid and volatile. *The names of all the alkaloids end in "ine."* The alkaloids are so called because they act like alkalies, in uniting with acids to form salts. *The salts have the same effects as the alkaloids but are much more soluble and are the preparations commonly used in medicine. Both the alkaloids and their salts are precipitated by tannic acid and oxidized by potassium permanganate solution.* Hence, these substances may be used as antidotes for alkaloid poisoning.

The chemical formulas of the alkaloids are very complex and of value only to chemists and research workers. The structural formulas of those used in medicine are given in the United States Pharmacopoeia.

In recent years, important advances have been made in our knowledge of the constitution of the alkaloids and many of these substances have been obtained synthetically. In contradistinction to the true or natural alkaloids, a certain number of substances not readily formed in nature but prepared artificially in the chemical laboratory have been termed *artificial alkaloids*. Antipyrine and acetanilid are examples of artificial alkaloids, which resemble the natural alkaloids in their physical action.

3. Carbohydrates

Carbohydrate food supplies more than two-thirds of the energy required by the human body. In addition, carbohydrates are important in medicine.

The greater part of plants consists of carbohydrates, which in the animal economy are important chiefly as foods. As a rule, they have the formula $(C_nH_{2n}O_n)_x$. Since the proportion of hydrogen to oxygen is the same as in water, the term *carbohydrate* originated through the erroneous conception that carbohydrates were composed of carbon with water which might be written $C_6(H_2O)$. While in the majority of cases hydrogen and oxygen are in this proportion, in other cases, as in rhamnose $C_6H_{12}O_5$, they are not. Again, in many substances, not carbohydrates, such as lactic acid, $C_3H_6O_3$, and acetic acid, $C_2H_4O_2$, the hydrogen and oxygen are in the same proportion as in water. Carbohydrates are more exactly aldehyde or ketone derivatives of polyatomic alcohols. Individual carbohydrates used in medicine will be discussed later in the book.

4. Gums

Classification of Gums.—For the present the classification of gums, as based on their solubility in water, is as follows:

1. Gums completely soluble in water, such as gum acacia.
2. Gums partially soluble, such as tragacanth.
3. Mucilages and pectins which swell to form a jelly.

Many natural gums are mixtures and do not fit well into this classification. Some authors regard gums as decomposition products of cellulose due either to nutritional disturbances or to bacterial action.

Acacia (Gum Arabic), U. S. P., is the gummy exudation from *Acacia senegal* and other African species of *Acacia*. It occurs in pale yellow, opaque, brittle, inodorous tears or fragments, which are soluble in water (1:2) but practically insoluble in alcohol. It contains arabic acid in combination with potassium, calcium, and magnesium.

Uses.—Acacia and its mucilage are used as demulcents and suspending agents in making emulsions and mixtures. It enters into chalk mixture, compound mixture of glycyrrhiza, emulsion of almond, emulsion of cod-liver oil, emulsion of oil of turpentine, troches of cubebs, and several pills. The mucilage of acacia, and the syrup are used to suspend insoluble, and to disguise the taste of unpleasant, drugs.

Acacia preparations are used chiefly as demulcents. Bayliss recommended that when normal saline was injected intravenously in shock and after hemorrhage, it should be suspended in 5 to 6 per cent acacia to hold it longer in the circulation. Special purified preparations should be employed for intravenous administration to prevent serious reactions.

Gum Tragacanth, U. S. P., a gummy exudation from *Astragalus gummifer*, consists of 8 to 10 per cent of soluble potassium, magnesium, and calcium salts, together with tragacanthin or bassorin. Tragacanth swells on the addition of water and gradually forms a cloudy gelatinous mass but does not dissolve in it. On further addition of water it forms an emulsion which is widely used as the basis for a greaseless catheter lubricant, and for application on chapped skin.

Mucilage.—(< *Mucilago*, moldy juice < *muceo*, to be moldy < *mucus*, mucus.) The term *mucilage* is applied to substances which in water form a slimy liquid. Mucilage is distributed widely in plants, but is especially abundant in the phanerogams (flowering plants).

The composition of mucilage is not definitely known, but it is related to cellulose and to arabin.

Mucilages vary in composition. They appear to be condensation products of various sugars (galactose, mannose, glucose, xylose, arabinose) and on hydrolysis give sugars only. In this respect mucilages differ from gums, which on hydrolysis yield sugars and also other substances. Mucilages are distinguished from pectic substances by the fact that mucilages do not gelatinize.

5. Glucosides

Glucosides are active principles which upon hydrolysis yield a sugar and one or more other substances. A general term applied to the nonsugar part of the hydrolyzed glucoside is "aglycone" or "a-glucone." The carbohydrate molecule is not necessarily essential for the action of the glucoside and may be removed by hydrolysis to liberate the active *aglycone*. Two important glucosides are digitalin and strophanthin. Glucosides are usually colorless bitter substances extracted from the plant with water and alcohol. The names of glucosides all end in "in."

6. Saponins

Saponins are glucosides found in various plants such as sarsaparilla, quillaja bark, serpentaria or snake root, etc. The name is derived from their behavior with water with which they form an opalescent fluid which froths, when shaken, like a solution of soap, if even $\frac{1}{1000}$ part of the saponin be present. Saponins are nonabsorbable, hence act only locally and are powerful gastrointestinal irritants.

7. Neutral Principles and Bitter Principles

Besides acid and basic substances, and substances that belong to a definite class of compounds, such as glucosides, plants may contain chemically neutral substances that, so far, belong to no definite chemical group. Some place bitters in this class. It is better, however, to retain the name "bitter principles" for those substances that are neutral, active, and which cannot be placed in some definite chemical group. The most important is picrotoxin.

8. Oils

The term oil is applied to a large number of liquids characterized by being insoluble in water and highly viscous. Their greasy feeling is due to these properties. The oils used in medicine are of two kinds: fixed and volatile.

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forms. The following are the general characteristics of the resins: at ordinary temperatures, they are solid, translucent and for the most part colored, although some are colorless and transparent. The rosin used by violinists is an example of a solid resin. A few are devoid of odor, while others give off an aromatic fragrance due to the admixture of volatile oil. In the crude state they are noncrystalline and brittle; when pure, several of them may be obtained in crystalline form. They melt at low temperatures, and are inflammable, burning with a white, smoky flame. Resins are insoluble in water; soluble in alcohol, ether and various oils. Many of them possess acid properties in which case their alcoholic solutions redden litmus. These resins combine with the alkalies and form frothy, soaplike solutions in alkaline lyes. Resins are local irritants and are most commonly used in medicine as cathartics, irritants, or local stimulants.

10. Oleoresins (Oleoresinae)

Oleoresins are thick liquid preparations consisting of volatile oils and resins extracted from vegetable substances by ether, acetone or alcohol. The only important one in medicine is the oleoresin of male fern—*Oleoresina Aspidii*. They are generally obtained by making incisions into the wood of trees which produce them; sometimes, however, they exude spontaneously, and in other cases require to be extracted from the wood with hot alcohol or other solvents. The crude resins are separated from the volatile oils by distillation.

11. Balsams

Resins also form important constituents of the substances known as *gum resins*, of which myrrh and asafoetida are examples, and are contained in the so-called *balsams*, a class of liquid or semisolid products including benzoin, storax, and the balsams of Peru and Tolu. These are resins which contain benzoic or cinnamic acid.

12. Tannins

Tannins are complex phenolic substances of widespread occurrence in plants. Practically every group of plants contains species which bear tannin. Tannins are especially abundant in the nutgalls on oak trees, sumach leaves, acacia, catechu, hemlock bark, krameria, etc. Their chemical structure is not well known, but they contain phenolic acids. They form insoluble precipitates with alkaloids and proteins and hence are used largely for their astringent effect.

A. Volatile or Essential Oils

Volatile or essential oils are liquids which give the peculiar odor to plants. Their composition varies widely. The various types are as follows: terpenes or hydrocarbons of the general formula $(C_{10}H_{16})_n$; certain esters, aldehydes, ketones, and phenols (substances composed of carbon, hydrogen, and oxygen) and finally, certain substances containing sulfur or nitrogen among their elements; e.g., mustard oil. All of these substances are soluble in alcohol, ether, petroleum, and certain other organic solvents. Some of them have been prepared synthetically but the greater number are still obtained from plants by some suitable process.

Because of their aroma, the volatile oils are valuable as flavoring agents; because of their volatility and consequent power of penetration, they are irritant, mildly stimulant and antiseptic. The irritant action of mustard and camphor is due to the volatile oil which they contain. The value of oil of peppermint in colic is due to its slight stimulation of the mucous membrane of the alimentary canal.

Each oil is found most profusely in a definite part of the plant; e.g., oil of orange in the rind of the fruit, oil of cinnamon in the bark, oil of rose in the petals.

Some oils, such as turpentine, juniper, lemon, and peppermint, exist as such in the plant. Others, such as oil of mustard and oil of bitter almond, do not exist free, but are liberated by the action of an enzyme from their combination. Others, like creosote, oil of tar, oil of juniper tar, are developed by destructive distillation. These are called empyreumatic oils (*empyros*, fire; *empyreuma*, disagreeable odor).

B. Fixed Oils

Fixed oils are those which do not evaporate easily and which upon hydrolysis yield fatty acids and glycerin. Some of the fixed oils are used for food; others are used for their soothing effect on skin or mucous membranes. In the case of castor oil the medicinal effect as a cathartic is obtained from the fatty acid produced by hydrolysis. Other examples of fixed oils are cod-liver oil, croton oil, and chaulmoogra oil.

9. Resins

Resins are a class of solid or semisolid substances mostly of vegetable origin. They form the sap of certain trees. Although widely divergent in chemical behavior, the resins contain only the elements carbon, hydrogen, and oxygen combined in a confusing variety of

CHAPTER X

ANTISEPTICS AND DISINFECTANTS

Very early in the history of mankind it was found that certain gums, balsams and resins had the power to prevent decay in the bodies of the dead, and today the Egyptian mummy is an evidence of the efficiency of the materials used. Some of these substances were also used for healing wounds, but it was not until the latter part of the nineteenth century when Pasteur made his astounding discoveries regarding the germ theory and Lister, in consequence, began the systematic use of carbolic acid in his surgical work that antiseptics came into general use.

The word *antiseptis* means *against sepsis*. Sepsis is the poisoning of the system by the introduction of toxic substances or pathogenic organisms into the blood stream. An *antiseptic* then may be defined as a substance which inhibits the growth of microorganisms. A *disinfectant* is a substance which *destroys bacteria** and renders harmless objects, places or materials containing pathogenic bacteria. A disinfectant differs from an antiseptic in not being intended for use upon the living body, for drugs that destroy germ cells also destroy living tissues. Hence, many substances are used as disinfectants which are not suitable for use as antiseptics; others are disinfectants in strong solutions and antiseptics in weaker solutions; still others are too weak in any solution to destroy bacteria but are effective in retarding their growth. Thus the germicidal efficiency of any solution depends largely on: •

1. *Its strength.*
2. *The length of time* the substance is in contact with the infected material or tissue.
3. The amount of organic matter present.
4. The temperature of the solution.
5. The degree of ionization—ionic action.

The term *germicide* is also applied to substances which kill microorganisms. *Deodorants* are agents used to destroy offensive odors. A *bacteriostatic* agent is one that tends to retard or suspend temporarily the growth of microorganisms.

*The term anti-infective is applied to any drug that rids the body of any living organism. See Systemic Anti-Infective Drugs in Chapter XXX.

13. Enzymes

Enzymes are the active principles of a number of vegetable and animal products used in medicine. Their chemical composition is unknown but they are rather easily destroyed by moist heat. Trypsin of the pancreatic juice and pepsin of the gastric juice are good examples of enzymes.

14. Hormones

Hormones are active principles of glandular secretions. Adrenalin of the adrenal gland, pitressin and pitocin of the pituitary gland, and insulin of the pancreas are hormones and influence the growth, development, and normal metabolism of the individual.

The most common use of phenol is in a 5 per cent solution for disinfecting instruments and utensils, bed linen and clothing, sinks, toilets, floors, etc., since it does not stain or otherwise injure fabrics, wood, paint, or metal.

It is also employed as an antipruritic in a simple aqueous solution or as an ointment or as a compound lotion of calamine.

Phenol is used as a standard for measuring the efficiency of other disinfectants, particularly those of the phenol group. The relative power of a disinfectant as compared with that of phenol is known as the phenol coefficient (P/C). A disinfectant having twice the germicidal efficiency of phenol, for example, has a phenol coefficient of 2.

2. Cresol or Methyl Phenol.—Cresols are phenols in which one of the hydrogen atoms in the benzene ring has been replaced by CH_3 . Cresol is similar in its origin and germicidal action to phenol. It is a thick, heavy, straw-colored liquid with a phenol-like odor. It is only slightly soluble in water but is soluble in liquid soap. It has a phenol coefficient varying from 2 to 3.

Liquor Cresolis Saponatus or Saponated Solution of Cresol, U. S. P., is a 50 per cent solution of cresol in vegetable oil. It is used in $\frac{1}{2}$ to 1 per cent solutions for vaginal douches and irrigations, in 1 to 2 per cent concentrations for cleaning the hands and in 2 to 5 per cent solutions for disinfecting body excretions, sinks, toilets, etc. Several preparations similar to the compound solution of cresol are sold under some trade name such as *lysol*, *creolin* and *kresol*.

Lysol is a mixture of cresol and linseed oil soap. It forms a milky emulsion in water but is more soluble than pure cresol. It has many uses in both the hospital and the home. Its action is not hampered by the presence of organic material and therefore is a valuable disinfectant (2.5%) for human excreta, sputum, contaminated utensils, bed linens, etc. It is poisonous and should be used for external purposes only.

3. Resorcinol, U. S. P., occurs as colorless needle-shaped crystals with a faint aromatic odor. It resembles phenol in its antiseptic action but is less toxic, irritating, and caustic. It is usually employed as an ointment or lotion in strengths varying from 1 to 10 per cent and is used for a number of skin diseases.

Hexylresorcinol was introduced as a urinary antiseptic. Much of its bactericidal efficiency is due to its low surface tension. Its activity, however, is adversely affected by the presence of organic material. Hexylresorcinol solution is a 1:1000 solution of hexylresorcinol in glycerin, 30 per cent, and water, 70 per cent. It

Mode of Action of Chemical Disinfectants

The chemical disinfectants owe their germicidal power to the reactions which they enter into with the protoplasm of the bacterial cell. They may be local or systemic in action.

1. Some disinfectants act as oxidizing agents, liberating nascent oxygen which combines with the bacterial cell and destroys it; as for example, potassium permanganate.

2. Others combine chemically with the constituents of the cell, as bichloride of mercury and iodine. This is true of the salts of the heavy metals.

3. Others dissolve or kill the proteins of the cell, as the acids and alkalies.

4. Still others hydrate or dehydrate the bacterial cell, in conformity to the law of osmosis, as do the strong salt solutions.

I. Chemical Agents Used

A. Coal Tar Group

1. Phenol (Carbolic Acid, C_6H_5OH), U. S. P., commonly known as carbolic acid, is chemically hydroxy benzene, and belongs to the group known as phenols which are derived from coal tar by the process of distillation. Phenol occurs in white, needle-shaped crystals, which may become pinkish on standing.

Phenol Liquefactum, U. S. P. Phenol is liquefied by adding about 5 parts of water. It contains not less than 88 per cent by weight of pure phenol. It is actually a solution of water in phenol. Phenol is soluble in water, 1:15. It is antiseptic, germicidal, and escharotic. When applied to a wound, phenol solutions coagulate the blood and protein and form a pellicle over the surface. Since this pellicle may protect the germs in the deeper tissues, it may do more harm than good. It is but little used as an escharotic. A solution of phenol applied to the skin produces at first a burning sensation accompanied by diffuse redness of the surface. If the solution is strong, the part at once becomes painful and then bleached and numb so that the sense of touch is destroyed; if application is prolonged, the skin and underlying tissues are destroyed and gangrene results. Absorption may also take place and produce severe toxic symptoms. Phenol burns on the skin may be treated with alcohol, with which it combines more readily than it does with living tissues.

It is thought that phenol reacts with bacterial proteins to form insoluble albuminates. It is effective even in the presence of organic matter.

The most common use of phenol is in a 5 per cent solution for disinfecting instruments and utensils, bed linen and clothing, sinks, toilets, floors, etc., since it does not stain or otherwise injure fabrics, wood, paint, or metal.

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is employed as a general antiseptic, but it has proved to be quite irritating to tissues and some people exhibit a marked sensitivity to its application. It is one of the efficient anthelmintics of present-day use.

B. Triphenylmethane (Rosaniline) Dyes

Gentian Violet is a mixture of pentamethylpararosaniline and methylpararosaniline chlorides (Methylrosanilinae, U. S. P.); also called methyl violet or crystal violet. It is soluble in 25 parts of water, and in 10 parts of alcohol.

Action and Uses.—It is bactericidal in water, and is said to be more so in the presence of albuminous fluids.

Dosage.—For direct application, a solution of from 1 in 500 to 1 in 1000 may be employed for instillation. For intravenous use, 5 mg. of body weight may be injected in 0.5 per cent dilution. Such use has been employed in encephalitis, septic endocarditis, and septicemia, but the use of sulfanilamide now is more promising. For Strongyloides infection, a dose of 0.03 Gm. is used.

Some antiseptics are very efficient in the absence of protein but rapidly lose their value in its presence. Protein does not affect all drugs to the same extent. Flavine or acriflavine is said to be less affected than others.

C. Salts of the Heavy Metals

1. **Mercuric Chloride, U. S. P.** (Bichloride of Mercury or Corrosive Sublimate), is a white crystalline solid, moderately soluble in water. It is usually sold in tablets in which the mercuric chloride is mixed with sodium chloride to make it more readily soluble. mercuric chloride is extremely poisonous. For this reason every precaution is taken to prevent mistakes in its use. The tablets are angular in shape and are stamped with skull and crossbones and the word "poison." They are colored blue to prevent their solutions being mistaken for water. Each tablet contains $7\frac{1}{2}$ grains (0.5 Gm.) of mercuric chloride, so that one tablet dissolved in a pint of water makes a 1:1000 solution. Mercuric chloride is a powerful germicide. In aqueous solution it ionizes and the mercury ions combine with the protoplasm of the bacterial cell. A 1:1000 solution kills all nonspore-bearing bacilli in one-half hour; a solution as weak as 1:300,000 inhibits the growth of many bacteria.

It is used chiefly in a 1:1000 solution as a disinfectant for the hands; and occasionally on wounds and mucous membranes in a concentration of 1:20,000 to 1:2000.

Although mercuric chloride is an effective germicide, it has many disadvantages: it is poisonous if absorbed, ineffective as a disinfectant in the presence of albuminous materials, corrosive to many metals, and irritating to the skin.

2. Merbromin, N. F. (Mercurochrome) is a complex compound of mercury and bromide. It is a nonirritating moderately active antiseptic. The aqueous-alcohol-acetone solution called surgical solution of merbromin is more rapid in its action than the aqueous solution and may be used as a skin disinfectant. A 1 per cent aqueous solution is used to treat urethritis and cystitis as well as infections of the eye and the ear. A 2 per cent solution is used as a skin antiseptic. The intravenous use of mercurochrome is not recommended.

3. Merthiolate, N. N. R.—Merthiolate is another organic mercury compound containing approximately 50 per cent mercury. It is germicidal and fungicidal for many organisms but sterilization is not necessarily accomplished, especially if spore-forming organisms are present. It is much less toxic than mercuric chloride.

Merthiolate occurs as a light cream-colored powder and an inert dye is added to it to give it color.

It is used for the disinfection of instruments in a 1:1000 aqueous solution; as a skin disinfectant in the form of the tincture 1:1000; for minor wounds and abrasions in the aqueous form 1:1000, and for irrigation of mucous membranes in concentrations from 1:2000 to 1:5000.

It is being used with increasing frequency as a skin disinfectant.

4. Metaphen, N. N. R., is used only in the form of its sodium salt. It contains between 56 and 57 per cent mercury in organic combination. Metaphen has an orange red color. It is said to be relatively nonirritating to skin and mucous membranes; it does not corrode metals or instruments and does not injure rubber.

It is used in the treatment of gonorrheal infections of the eye, and for disinfection of the skin, surgical instruments, and rubber. It is not so effective if pathogenic spore-forming organisms are present.

Metaphen is used in the following strengths:

For instruments	1:1000
For the skin	1:2000
For urethral irrigations and for the eye	1:5000

5. Mercuric Cyanide, N. N. R., and Mercuric Oxycyanide, N. N. R., are used like bichloride of mercury. They are less irritating to the skin and do not corrode metals. The former is used in 1:4000 to 1:2000 solutions; the latter in 1:500 solution.

6. **Mercurial Ointments.**—Mercury is used in a variety of ointments and lotions, the most important of which follow. **Strong Mercurial Ointment**, U. S. P., contains about 50 per cent of metallic mercury in a base of prepared suet, benzoinated lard and 2 per cent oleate of mercury. **Mild Mercurial Ointment** (Blue ointment), U. S. P., contains 40 per cent of stronger mercurial ointment (10 per cent of metallic mercury) in a base consisting of equal parts of petrolatum and ointment. It is most commonly used on sores and eruptions of syphilitic origin, and in the form of an inunction ranks next in antisiphilitic efficiency to intramuscular injections. **Ointment of Ammoniated Mercury** (White Precipitate Ointment), U. S. P., contains 5 per cent of ammoniated mercury in a base of white ointment, and hydrous wool fat. Ammoniated mercury is also used in ointments of 2 to 10 per cent as antiseptics and local stimulants in suppurating dermatitis, seborrhea, and psoriasis. **Ointment of Yellow Mercuric Oxide**, U. S. P., contains 1 per cent of yellow mercuric oxide. It is employed as an antiseptic and stimulant chiefly in the treatment of inflamed and sore eyelids and stytes.

7. **Silver Nitrate**, U. S. P., is made by dissolving silver in nitric acid. It occurs in flat transparent crystals which become gray or grayish black on exposure to light in the presence of organic matter. It is odorless and has a bitter, strongly metallic taste. It is very soluble in water (1:0.4) and soluble in alcohol (1:30). It ionizes vigorously and therefore is a powerful disinfectant. Silver nitrate reacts with soluble chlorides, iodides, and bromides and for this reason solutions of silver nitrate should always be made with distilled water. A 1:1000 solution kills most bacteria in a very short time; a 1:10,000 solution is antiseptic. Weak solutions are astringent to mucous membranes and strong solutions are caustic when applied to mucous membranes and in some cases to normal skin.

Silver nitrate is used on inflamed mucous membranes and ulcerated surfaces. For diseases of the conjunctiva, solutions varying in strength from 0.2 to 2 per cent may be used. To prevent the development of gonorrheal conjunctivitis in the newborn, a drop of 2 per cent solution is instilled into each eye as soon as possible after delivery. A strength of 4 per cent has been used, but it is dangerous, because this strength in a short time will kill tissue and may thus permit the gonococcus to enter and spread into deeper tissues. Blindness has been caused in this way. To stop the action if too much has been used, wash with physiologic saline.

Solutions containing 2 to 10 per cent of silver nitrate may be applied to the pharynx. For the urethra it is employed in the strength of 1:10,000 to 1:2000 and a solution of 1:5000 strength may be injected into the bladder.

State Boards of Health usually give silver nitrate solutions free to doctors to be used in the prevention of gonorrheal ophthalmia. This is usually put up in capsules made of beeswax. On standing in the capsules the silver tends to unite with the wax, and the acid liberated increases the pH and renders the solution irritating. It may change from a pH of 6.8 to pH 2.2. This is enough to cause severe inflammation of the conjunctiva; solutions, therefore, should be freshly prepared.

Fused Silver Nitrate (Lunar Caustic, Moulded Silver Nitrate), U. S. P., is a white solid generally used in the form of pencils or cones. It is applied as a mild caustic to wounds, ulcers, and granulation tissue. It should be moistened before use and, to avoid blackening the fingers, should be held with forceps. It may be fused on a probe for application to parts that are difficult of access. The mucous membranes to which solutions of silver nitrate are applied should receive a preliminary cleansing to remove mucus, pus, food, etc., which would interfere with the action of the drug.

Colloidal Silver Preparations are formed by the combination of silver with protein. They do not precipitate proteins and are therefore nonastringent and almost nonirritant. The germicidal effect of colloidal silver preparations is due to the gradual liberation of silver ions. Colloidal preparations are nonirritating and do not precipitate protein.

Strong Silver Protein. The U. S. P. XII listed a preparation called strong silver protein, although it did not contain as much silver as the mild silver protein of U. S. P. XIII. The so-called strong preparation has been deleted. This is a step in the right direction. There is no need of more than one or two preparations of any drug. All silver preparations act because of silver ions, and it is very questionable if any of them excel the use of silver nitrate, if properly diluted. If a colloidal preparation is thought necessary, the mild preparation of the U. S. P. is quite adequate.

Mild Silver Protein, U. S. P., is a colloidal silver preparation containing 19 to 23 per cent of silver. It occurs as dark brown, lustrous scales or granules which are freely soluble in water, forming deeply

colored colloidal solutions. It is also soluble in glycerin. Mild silver protein differs from the strong in being entirely nonirritant; it is also less active as an antiseptic but is more soothing. It is usually employed in concentrations of from 10 to 25 per cent. *There are many colloidal silver preparations on the market, the most important of which are argyrol, argyn, cargentos, silvol, and solar-gentum.*

The terms *strong* and *mild* refer to the relative antiseptic values and not to the amount of silver they contain; for the *strong* contains about 8 per cent silver and the *weak* about 20 per cent. *The antiseptic value depends on the extent of ionization in any given liquid.* Mild protein silver preparations should be freshly made and dispensed in amber-colored bottles.

D. The Chlorine and Iodine Group

Chlorine

Chlorine is a nonmetallic element which occurs in the form of a greenish yellow gas. It has an intensely disagreeable odor, and attacks the membrane of the nasal passages and lungs, producing effects something like those of a bad cold. Chlorine is one of the most efficient disinfectants known, especially in the presence of water. *The chlorine combines with the hydrogen of the water, liberating nascent oxygen, which oxidizes and kills the bacteria.* Its germicidal action is also due to the reaction of chlorine with unsaturated components of the germ plasm. Chlorine may directly attack the protein molecule and replace hydrogen in the amino groups yielding chloramines.* One part of nascent chlorine in 1,000,000 parts of water will destroy most pathogenic bacteria in a few minutes. Chlorine is also an efficient deodorant.

Chlorinated Lime is made by the action of chlorine on calcium hydroxide. It occurs as a white or grayish white granular powder, having a chlorinelike odor. It contains not less than 30 per cent of available chlorine; that is, chlorine which is set free by the action of any common acid. It is one of the cheapest and most widely used disinfectants. Its chief use is to disinfect infected material such as feces and other excreta. A 5 per cent solution is suitable for ordinary use. To disinfect excreta, equal volumes of excreta and 1:5 solution should be mixed thoroughly and allowed to stand for one hour.

It is used extensively as the source of chlorine for treating contaminated drinking waters. The fresh solution of about 0.5 per cent

*Davison, F. R.: *Synopsis of Materia Medica, Toxicology and Pharmacology*, St. Louis, 1944, The C. V. Mosby Co., p. 148.

should be added to the water treated in the proportion of about 25 gallons per million gallons of water.

Chlorine is a strong bleaching agent and should not be used on colored fabrics. It also corrodes metals.

Diluted Solution of Sodium Hypochlorite (Modified Dakin's Solution), N. F., is an aqueous solution of chlorine compounds of sodium made by dissolving chlorinated lime and exsiccated sodium phosphate in water. The solution has to be carefully prepared to contain exactly the required amount of available chlorine, from 0.43 to 0.48 per cent, and to be of the required degree of alkalinity. It is nearly neutral in reaction and is practically isotonic with the blood. It dissolves blood clots, pus and dead tissue and thus has a cleansing effect in wounds. *It does not irritate wounds but may burn the surrounding skin which must be protected by a thick layer of petrolatum.*

The chief use of Dakin's solution is for the disinfection of wounds by the continuous irrigation method. The solution is allowed to flow into the wound through fine rubber tubes in the sides of which holes have been punched so that the solution is brought into contact with all surfaces of the wound. The apparatus is arranged with a stop cork so that the solution is allowed to flow in at regular intervals. This is the Carrel-Dakin method of treating wounds.

Chloramine-T, N. F., is chemically Sodium Paratoluenesulfon-chloramide. It occurs as white or yellowish crystalline powder, which has a slight odor of chlorine and is very soluble in water.

Chloramine is very similar in action to Dakin's solution. It is more stable and less irritating, but does not have the solvent action of the latter. It is employed in 0.1 to 4 per cent solutions. On wounds it is used in 1:2 per cent solutions by the Carrel-Dakin method.

Dichloramine-T, N. F., is chemically Paratoluenesulfondichloramide. It contains about 29 per cent of active chlorine and is commonly known as "dichloramine T." It is a yellowish crystalline powder, having a faint odor of chlorine. It is almost insoluble in water but is soluble in chlorinated paraffin. Solutions prepared in this way produce a gradual, sustained antiseptic action. Dichloramine is more irritating than chloramine, but also more solvent. It is used chiefly for the disinfection of wounds and to some extent in the treatment of diseases of the nose and throat. Dichloramine dissolved in chlorinated paraffin is used in concentrations of from 2 to 10 per cent. When used as a spray, a 2 per cent solution is employed; for application to infected wounds, a 3 to 10 per cent solution is used.

The T in these compounds refers to toluene. They are compounds of paratoluene.

Chloroazodin, U. S. P. (Chlorozodinum, Azochloramid). Contains about 38 per cent active chlorine and is unstable in light. It has a bright yellow color and is only slightly soluble in water and glycerin. It is stable and soluble in glyceryl triacetate. It appears to have a relatively low toxicity and greater bactericidal activity than Chloramine-T, especially in the presence of organic material.

Solution of Chloroazodin, U. S. P.—This substance resembles Dakin's solution as well as Chloramine-T and Dichloramine-T. Solutions of chloroazodin are useful for dressing, packing, and irrigating infected wounds and cavities.

Chloroazodin is recommended in concentrations of 1:1500 and 1:3000 in isotonic salt solution. Solutions of 1:2000 in olive oil are used for topical application to mucous membranes.

Iodine

Iodine, U. S. P., is very slightly soluble in water but is soluble in alcohol and in an aqueous solution of potassium iodide. Iodine is also official in the forms of *Tincture of Iodine* and the *Compound Solution of Iodine* (Lugol's Solution). The tincture of iodine is a diluted alcoholic solution containing iodine, 2 per cent, sodium iodide, 2.4 per cent. *Lugol's Solution* is a solution in water of iodine, 5 per cent, and potassium iodide, 10 per cent.

Iodine irritates the skin, causing a sensation of heat and itching and in concentrated solutions will cause blisters. Because of this action, iodine is sometimes used as a counterirritant. It penetrates into the deeper layers of the skin and combines chemically with some of the constituents of cells. It is therefore an effective disinfectant for wounds and for preparing the skin for operations. For the former purpose a 3 per cent solution of iodine should be applied to the skin about the wound and pieces of gauze soaked in the same solution used in the wound itself. For the surgical preparation of the skin the tincture or a 3 per cent alcoholic solution is painted over the area to be disinfected. The skin must be thoroughly dry before application of the iodine to avoid blistering.

Mild Tincture of Iodine (*Tinctura Iodi Mitis*), U. S. P., contains 2 per cent of iodine and 2.4 per cent of sodium iodide in diluted alcohol. The iodide is added to increase solubility in water.

Iodine solutions are usually applied by means of a swab. On a sensitive skin an iodine application may be painful and even blister.

ing, and care should be taken not to apply a second coat unless it is known that it will produce no untoward results.

Since iodine is volatile, its solutions should not be exposed to the air except during immediate use.

Iodine stains the skin and linen brown. The stains can be removed with alcohol or ammonia, and from fabrics with boiling water.

E. Oxydizing Agents

1. **Solution of Hydrogen Peroxide**, U. S. P., is a 3 per cent solution of H_2O_2 in water. It is a colorless, odorless liquid, which deteriorates on standing. It should be kept in a cool, dark place stoppered with a thick plug of cotton.

In contact with organic matter, such as pus or blood, hydrogen peroxide is rapidly decomposed, liberating nascent oxygen which destroys the bacteria with which it comes in contact and disinfects the tissues. At the same time, the effervescence which occurs tends to clean the wound of dead tissue or pus. Since any organic matter easily reduces hydrogen peroxide and renders it inert, its germicidal power is limited but is of great value as a cleansing agent for suppurating wounds and abscess cavities. The solution is usually diluted with 1 to 4 parts of water before use. It must be used with great care in deep cavities, because enough gas may be liberated to cause pain by pressure, or to rupture the walls and aid in the spread of infection. A free opening for the escape of foam and gas should be provided.

2. **Potassium Permanganate**, U. S. P., occurs as dark purple crystals which are soluble in water (1:15). It decomposes in contact with organic matter and liberates oxygen, which combines with bacteria and inhibits their growth or destroys them. It is irritant, astringent, and deodorant. It is used as vaginal and urethral douches in solutions of 1:5000 to 1:1000; for irrigation of suppurating wounds in 1 to 3 per cent; for disinfection of the hands in 3 per cent solutions (the hands are kept in the solution until they are mahogany brown); as an antidote for phosphorus poisoning and as a caustic in snake bites.

The brown stain of potassium permanganate may be removed with oxalic acid, dilute hydrochloric acid, and lemon juice.

If a solution turns dark brown, it is an indication that the permanganate has become inert.

F. Miscellaneous Agents

1. **Nitrofurazone**, N. N. R. (Furacin, Eaton Labs.), is a derivative of furfural and possesses bacteriostatic and bacteriocidal properties.

It is not soluble in less than 5,000 parts of water. It is inhibitory in solutions of 1:200,000 to 1:300,000 and bactericidal at 1:50,000 to 1:75,000.* It is effective against a number of gram positive and gram negative organisms. It is used for topical application in prophylaxis and treatment of superficial, mixed infections common to contaminated wounds, burns, ulcerations, and certain diseases of the skin.

Although Nitrofurazone in some instances causes a sensitivity to develop from repeated topical application, systemic toxicity due to absorption of the compound is unlikely. Its internal use, however, is not recommended.

Nitrofurazone may be applied in the form of an ointmentlike base containing a concentration of 1:500. It is applied to dressings or directly to the infected areas. The base liquefies at body temperature and for that reason may require a covering to maintain contact with a specific area.

Nitrofurazone upon exposure to light turns dark brown. This is not associated with any undesirable effects and may be avoided if a light covering is applied.

2 Boric Acid, U. S. P., is mildly antiseptic and astringent and is usually soothing to the skin and mucous membrane. Externally it is used frequently as a dusting powder, either alone or combined with diluents such as starch or talcum, or with active substances such as salicylic acid or iodoform. It is also used in aqueous solutions of 2 to 4 per cent as a wash or lotion, especially for catarrh of the mucous membranes, pharyngitis, etc. It has been one of the commonest lotions for conjunctivitis. Boric Acid is an ingredient of many antiseptic solutions for washes and gargles such as Listerine, Glycothymoline, and Dobell's solution. Thiersch's Solution or borosol is a weak solution of boric acid containing salicylic acid.

Although boric acid is not very toxic, serious poisoning and deaths have resulted from its ingestion. Symptoms of poisoning include nausea and vomiting, diarrhea, abdominal pain, headache, weakness, visual disturbances, collapse, and possibly death.

With the advent of more effective germicides the use of boric acid is decreasing.†

Glycerite of Boroglycerin, U. S. P., is a glycerin solution of boroglycerin (boric acid combined with glycerin) containing between 47.5 and 52.5 per cent of boroglycerin.

*N. N. R., 1947, p. 81.

†Watson, E. H.: Boric Acid, J. A. M. A. 129: 333, 1945.

The Ointment of Boric Acid, U. S. P., contains 10 per cent of boric acid in a base of white ointment. It is mildly antiseptic but is used chiefly as a protective dressing.

3. Alcohol, U. S. P.—In the concentration of 70 per cent, it is markedly antiseptic and is often employed either alone or as tincture of green soap to cleanse the skin of the patient and the hands of the doctor. It is commonly used to prepare small areas of skin as for a hypodermic injection.

The Antiseptic Action of Alcohol.—In 5 to 10 per cent solution, alcohol inhibits the growth of bacteria. The optimum antiseptic action is exerted by 70 per cent solution. Bacteria may withstand exposure to absolute alcohol, but are killed by 70 per cent solution, the explanation being that strong alcohol probably forms an impenetrable film on the bacterium which prevents further penetration, while in the presence of water, penetration takes place. Many substances which are antiseptic in water are not effective when dissolved in alcohol because they are not ionized in alcohol. Alcohol has more important uses than its use as an antiseptic. At best, its action is rather slow and uncertain.

Propyl Alcohol.—See p. 209.

4. **Soft Soap** is commonly used in the form of "Tincture of Green Soap" or **Liniment of Soft Soap**, U. S. P., an alcoholic solution containing about 65 per cent of soft soap, perfumed with oil of lavender. (It is called "green" because it was first made from oils that contained chlorophyll-like coloring matter. Modern "green" soap may be colorless.) Soft soap has little antiseptic value, but is used primarily as a cleansing agent.

5. **Lime (Quicklime)** is a fairly active germicide. On account of its cheapness, it is much used as a disinfectant. It is especially useful for the disinfection of excreta. Freshly prepared milk of lime may be added in volume equal to that of the material to be disinfected, the mass thoroughly mixed and allowed to stand for two hours before disposal. A still better method of using it is to add enough quicklime to the excrement to make it boil. Milk of lime or whitewash is a serviceable application to privies and to the walls of infected rooms.

6. **Formaldehyde.**—Formaldehyde gas is a powerful parasiticide because of its penetrating power, but is active only in the presence of an abundance of moisture. The principal application of formaldehyde is in room disinfection.

Solution of Formaldehyde, U. S. P., known also by the proprietary name *formalin* is an aqueous solution containing 37 per cent of

formaldehyde. It is a clear, colorless liquid which, on exposure to air, liberates a pungent, irritating gas. The solution is strongly germicidal; a 1 to 2 per cent solution will kill ordinary bacteria in twenty to thirty minutes. Formaldehyde solution hardens tissue and a 4 per cent solution is used in histology for this purpose. It is also a deodorant.

Formalin is used chiefly for the disinfection of excreta, clothing, and rooms. An equal amount of 10 per cent solution should be used and allowed to stand for one hour. Soiled sheets and clothing may be immersed in a 5 per cent solution for one hour.

Because of the irritating fumes liberated by formalin, it should not be used on the body or in the sick room.

G. Detergents

1. **Benzalkonium Chloride**, U. S. P. (Zephirin Chloride—Winthrop), when employed in proper concentration, is an effective, relatively noninjurious surface disinfectant. It is germicidal for a number of pathogenic nonspore-forming bacteria and fungi after several minutes of exposure. Benzalkonium Chloride solutions have a low surface tension and possess keratolytic detergent and emulsifying properties. Solutions of soap reduce its germicidal activity unless well rinsed from the area to be disinfected. Seventy per cent alcohol serves to diminish the reaction of soap and the disinfectant and may well follow the use of soap and water scrub procedures before the application of the disinfectant.

Solutions of Benzalkonium Chloride have a relatively low level of toxicity under conditions of use for which they are recommended.

It is suitable for prophylactic disinfection of the intact skin and mucous membranes and in the treatment of superficial injuries and infected wounds when used in concentrations ranging from 1:40,000 to 1:1000. It is a local anti-infective.

Solutions of 1:1000 are used for preservation of metallic instruments and rubber articles. For disinfection of operating room equipment, 1:5000 may be used.*

2. **Phemerol Chloride**, N. N. R. (Parke Davis), is a detergent which exerts an inhibitory effect on the growth activities of commonly occurring bacteria and fungi. Tincture of Phemerol Chloride 1:500 and Aqueous Solution of Phemerol Chloride 1:1000 are used full strength as general germicides and antiseptics except for use in the nose and eye. For the latter the aqueous solution is used and diluted with four parts of water.

*N. N. R., 1947, p. 70

Suggestions for Study and Review

1. Define: antiseptic, disinfectant, germicide, deodorants.
2. Indicate some of the ways in which chemical disinfectants act.
3. Give the properties, actions and uses of phenol.
4. What preparations of phenol are most commonly used?
5. What is meant by the term phenol coefficient?
6. What are the properties, actions and uses of cresol?
7. For what purpose is picric acid most commonly used? In what preparations?
8. Give the properties, actions, and uses of resorcinol, acriflavine, gentian violet.
9. What are the synonyms for mercuric chloride?
10. How does mercuric chloride destroy bacteria?
11. What are the disadvantages of mercuric chloride?
12. What are the properties, actions and uses of mercurochrome?
13. Give the properties, actions and uses of silver nitrate.
14. What are the synonyms for fused silver nitrate? What are its properties and uses?
15. What are colloidal silver preparations? Name two official preparations; two commercial preparations.
16. Explain the germicidal action of chlorine.
17. What is the chief use of chlorinated lime?
18. What is another name for solution of chlorinated soda? What are its properties and actions?
19. How is the solution applied?
20. What two chemical preparations closely resemble the solution of chlorinated soda? Compare their actions and uses.
21. Name the official preparations of iodine.
22. What are the properties and uses of iodine?
23. Name two oxydizing agents. Discuss their action.
24. Give the principal uses of boric acid.
25. Name some of the antiseptic solutions of which boric acid is an ingredient.
26. Give the preparations and uses of lime.
27. What is the chief use of formaldehyde?
28. Give the properties and uses of solution of formaldehyde.
29. What are detergents? Mention some of the most recent detergents.

UNIT III

CHAPTER XI

PHARMACOLOGY AS RELATED TO THE NERVOUS SYSTEM

Because of the far-reaching influence of the nervous system which controls, directs, and coordinates the activities of organs and tissues of the body, such as the contraction and relaxation of muscles, secretion of glands, circulation of blood, mental processes and emotional reactions, it is thought advisable to place the study of drugs as they affect this system early in the course. Many of the drugs which may be studied exhibit a more selective action upon one part of the nervous system than upon another, and for that reason, the detailed discussion of each drug will be considered according to its major therapeutic effect. Understanding of drug action as it is related to the nervous system is dependent upon the understanding and mastery of items of knowledge of the anatomy and physiology of this system. The student nurse has already completed a basic course in this subject and hence is responsible for a systematic review.

Action of Drugs on the Central Nervous System

Drugs either stimulate or depress the nerve centers, thereby increasing or lessening the activity of the parts they control.

The entire brain may be stimulated or only certain areas of it. *When all the sensory areas are stimulated*, more numerous and more vivid impulses and impressions are received so that the patient is more alert, wider awake and more conscious or aware of his surroundings.

When the motor areas are stimulated, the patient is more active and restless; when overstimulated, impulses for action are so many and varied that coordination is lost and convulsions result.

When the speech area is stimulated, the patient becomes more talkative. If there is excessive stimulation, the speech becomes incessant and incoherent and results in delirium. These effects, however, may be due to depression of inhibition, or control, as in the case of alcohol, rather than to an actual stimulation.

Stimulation of the various centers of the medulla produces deeper and faster breathing, a faster and stronger or a slower pulse, increased blood pressure and frequent and profuse emesis.

The medulla contains the respiratory, emetic, vagus, vasomotor, and other centers. An action on the medulla is indicated by change in the function of any of these centers.

The spinal cord, which acts as a center for reflex action and also functions in the transmission of impulses to and from the brain, will be affected by drugs to the extent that the speed of transmission of impulses will be modified; reflex action will be increased or decreased, etc.

It is to be remembered that drugs cannot produce activities for which the cells are not biologically adapted. No new function will be produced but rather the already existing functions will be modified in some way.

CENTRAL STIMULANTS

Central stimulants are drugs which increase the activity of the brain, medulla, and spinal cord. They are used to counteract the depressant effects of such drugs as opium, morphine, and alcohol; to speed up the vital processes in conditions of shock and collapse. Drugs which are commonly used for their stimulating effect on the central nervous system are caffeine, atropine, and strychnine.

The Xanthines.—Caffeine, theobromine, and theophylline are methylated xanthines. They have a similar type of action but vary markedly in the intensity of their action on various structures. Theobromine and theophylline have slight action on the nervous system and will be discussed under diuretics and cardiac stimulants. Caffeine acts chiefly on the central nervous system.

Caffeine

Source.—Caffeine, U. S. P., is a white crystalline powder obtained for commercial purposes from tea dust or damaged tea leaves. It is the active alkaloid occurring in a number of plants used in different parts of the world as beverages, among them being coffee, the seed of the *Coffea arabica*; tea, the leaves of *Thea sinensis*; the kola nut of Central America; guarana, derived from the seeds of a Brazilian plant and from yerba maté or Paraguay tea. Tea contains from 1 to 5 per cent of caffeine; coffee, from 1 to 2 per cent. Tea contains 10 to 24 per cent of tannin. Coffee contains a very variable amount of caffeeo-tannic acid (Av. about 12 per cent) which is not very astringent.

Action and Result.—Caffeine in small doses stimulates the entire central nervous system, and especially the part associated with the mental faculties. Its action is a descending one. Small doses stimulate the higher centers, larger doses stimulate the cerebrum and the medullary centers, and still larger doses exhibit a progressive stimulation which involves also the spinal cord. As a result the mind is more alert and active, the memory is better, thought clearer, and spirits are higher. The sense of touch may be more discriminating, and the sense of pain more keen. The latter effect may not be desirable in the sick patient when it brings about keener realization of the gravity of an illness. Stimulation is not necessarily followed by depression except as it brings about exhaustion of natural reserves.

Respiration is quickened and deepened due to strong stimulation of the respiratory center in the medulla. This effect is particularly noticeable after parenteral administration of the drug or when the respiratory center has been subject to the depressant action of a narcotic. There is some stimulation of the vagus and vasoconstrictor centers of the medulla although partially masked by the peripheral action on the heart and blood vessels.

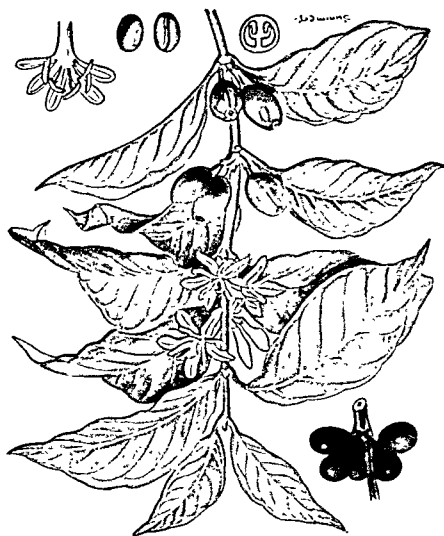
Large doses of caffeine bring about stimulation of the entire central nervous system including the spinal cord. There is first an increased reflex excitability which may with increasing dosage result in muscle twitching, especially in the limbs and face.

Caffeine exerts a direct stimulation on the myocardium which brings about both an increased cardiac rate and increased cardiac output. This effect is antagonistic to that produced by the central action on the vagus center, consequently a slight slowing of the heart may be observed in some individuals and an increased rate in others. The latter effect usually predominates after large doses. Overstimulation may cause a harmful tachycardia and cardiac irregularities.

Peripherally, caffeine depresses the smooth muscle of the blood vessels, thus causing vasodilation in contrast to the vasoconstriction produced by its central action. However, after therapeutic doses the peripheral action predominates and results in increased flow of blood and improved circulation. A slight and somewhat transitory elevation of blood pressure is sometimes noted.

Improved muscle tone and lessened susceptibility to fatigue have also been observed, but whether the action is a direct one on the striated muscle cells or whether the effect is produced by masking the sense of fatigue through cerebral stimulation is not fully understood.

PLATE III.—*Coffea arabica* (Coffee) (From Jackson *Pharmacology and Materia Medica*)
Experimental



Like the other xanthines, caffeine increases the flow of urine, but its action is relatively weak. The mode of action seems to be that of depressing the tubule cells and preventing reabsorption of fluid.

The metabolic rate is slightly increased after caffeine. An appreciable tolerance to certain of the effects of caffeine is readily established, although apparently not to the cerebral effects. Caffeine is also used to relieve fatigue, depression, and headache.

Administration.—The dose of caffeine is 0.2 Gm. (3 grains). A cup of beverage made from a tablespoonful (15 Gm.) of ground coffee contains 0.1 to 0.2 Gm. ($1\frac{1}{2}$ to 3 grains) of caffeine. The alkaloid may be given in the form of powder or in capsules or cachets.

Caffeine stimulates the output of pepsin as well as hydrochloric acid in the gastric juice.¹ Coffee therefore is usually contraindicated in the diet of patients with gastric and duodenal ulcer.

Caffeine is usually prescribed as Caffeine Citrate or Caffeine with Sodium Benzoate because they are more soluble than caffeine itself. Caffeine with Sodium Benzoate is usually given hypodermically while the citrated form is given orally. Caffeine may also be given in the form of a beverage either orally or by rectum. The caffeine content of an average cup of coffee is from 2 to 3 grains. Caffeine sometimes exhibits a local irritant action on the gastric mucosa resulting in nausea and vomiting or gastric distress. Sick people often do not tolerate coffee well as a beverage, especially if already slightly nauseated. Weak tea is often much better tolerated by the patient who is resuming oral fluids after anesthesia.

Symptoms of Overdosage.—Fatal poisoning by caffeine is rare, partly due to the fact that it is readily excreted as urea and also because a tolerance is developed. The fatal dose is presumably about ten grams. Toxic doses produce excessive irritability, restlessness, insomnia, nervousness, heart palpitation, profuse flow of urine, nausea and vomiting, headache, and heart palpitation, particularly in susceptible individuals. The more chronic symptoms of poisoning include insomnia, anxiety, and functional cardiac symptoms. The signs of chronic caffeine poisoning are more commonly seen among workers, like night nurses, who use coffee to keep awake and continue work when physically tired. The same symptoms of nervousness disappear when the overuse of coffee is stopped. The use of coffee to combat fatigue is like a whip to a tired horse, and its continued use is certainly questionable.

¹Roth, J. A., and Ivy, A. C.: *Am J. Physiol.* 141: 461, June 26, 1944.

Treatment.—Stopping the drug is usually sufficient treatment. Rest and quiet will also help and in some acute conditions a sedative such as a short acting barbiturate may be indicated.

Preparations and Dosage.—

Caffeine (Caffeina), U. S. P. Dosage: 0.2 Gm. (3 grains).

Caffeine and Sodium Benzoate (Caffeina et Sodii Benzoate), U. S. P. Dosage: Oral or intramuscular 0.5 Gm. (7½ grains).

Citrated Caffeine (Caffeina Citrata), U. S. P. Dosage: 0.3 Gm. (5 grains).

Uses.—

1. In the treatment of narcotic poisoning caffeine is effective in overcoming the depressant action of the narcotic. The direct action of caffeine on the respiratory center of the medulla is particularly valuable. For rapid effect caffeine with sodium benzoate is the preferred preparation because it may be given parenterally.

2 Caffeine is used frequently as a constituent of various headache remedies along with analgesic drugs. Some sufferers of migraine headache are relieved by an injection of caffeine and sodium benzoate. It is thought to have a beneficial effect on cerebral circulation.

3 Caffeine is used as a heart and respiratory stimulant in cases of collapse or syncope

4. Although all xanthines increase the flow of urine, caffeine is the least powerful. When caffeine is used for its diuretic action, caffeine citrate is the preparation of choice.

Camphor

Source.—Camphor, U. S. P., is a white, crystalline substance obtained from the camphor tree of China and Japan, or prepared synthetically.

Action and Uses.—Applied to the skin, camphor is a mild anodyne and counterirritant and is widely used in liniment form to relieve the pain of sprains or muscular rheumatism. Powders containing camphor are useful in itching conditions of the skin. Internally, it is antiseptic and carminative, and is used in mouth washes, gargles and nasal sprays for the treatment of infections of the respiratory tract and in solutions for dyspepsia and similar disturbances.

When camphor is absorbed into the blood stream, it stimulates the central nervous system, especially the centers of the medulla. It is therefore used as a circulatory and respiratory stimulant in cases of collapse and cardiac failure, but its action cannot be relied upon.

In toxic doses, camphor causes excitement, delirium and convulsions. The bromides are the physiologic antidotes.

Administration.—Camphor is used locally for its counterirritant effect in camphor, soap, and chloroform liniments. By mouth, it is administered in the form of the water, dose 10 cc. (2½ drams) and the spirit, dose 1 cc. (15 minims). Because of its antiseptic action, it is an ingredient of various antidiarrheic preparations. For its systemic effects, camphor is given hypodermically in doses of from 0.5 to 1 cc. (8 to 15 minims) of a 10 to 20 per cent sterile solution in olive or almond oil, repeated at short intervals. This preparation is sometimes called camphor in oil and should not be confused with camphorated oil.

Nicotinamide, U. S. P. (Nikethamide, Coramine, Diethyl Nicotinamide)

Nicotinamide is chemically related to nicotine and in some respects resembles its action. There is evidence that it stimulates the central nervous system, particularly the medullary centers. This action results in peripheral vasoconstriction and an increased depth and rate of respiration. The rise in blood pressure is sustained, especially when the lowered tension is due to depression of the central nervous system.

Nikethamide has been used as a respiratory stimulant and also as a cardiac stimulant. Claims have been made that it increases the coronary blood flow, but the evidence is inconclusive. It is also said to act as an analeptic, that is, it counteracts the anesthetic action following the action of central nervous system depressants. Like other derivatives of nicotinic acid, it has proved effective in pellagra therapy. The most effective avenue of administration seems to be the intravenous one, although it may also be given intramuscularly, subcutaneously, and orally.

Nicotinamide Injection, U. S. P., is about 100 per cent. Dosage depends upon the rate of administration. Range of dosage is from 1 to 3 cc. When doses larger than 3 cc. are given, the patient should be watched very closely. Large doses may cause respiratory failure.

Metrazol, N. N. R. (Pentamethylenetetrazol, Cardiazol)

Metrazol is a central nervous system stimulant which is chemically related to camphor but is said to be more stable and dependable than camphor. Metrazol stimulates the higher centers of the cerebrum and also all parts of the cerebrospinal axis. The vasoconstrictor, vagus, and respiratory centers of the medulla are stimu-

lated and reflex activity in the spinal cord appears to be increased, particularly in depressed states. It has been reported to be of value as a circulatory stimulant but its action on the heart and blood vessels is believed to be negligible.

In addition to being used in the treatment of poisoning by depressant drugs, it has been used in the treatment of mental disorders in doses sufficiently large to cause convulsive seizures. Results appear to be fairly promising, although it is difficult to determine adequately the value of this drug in this form of therapy. Since the treatment entails definite risks to the patient, it must be given by a specially prepared psychiatrist or in an institution where the patient will receive the necessary care.

Dosage: 0.1-0.3 Gm. ($1\frac{1}{2}$ -4 grains). Intramuscularly, subcutaneously, intravenously repeated as required—or orally several times a day.

Strychnine

Source.—Strychnine is an alkaloid derived from the seeds of *Strychnos nux vomica*, a tree grown in the East Indies. The nux vomica seeds are large, grayish, disc-shaped seeds which are very poisonous in their nature and are variously known as poison nut, dog button, and quaker button. The pharmacologic action of nux vomica is due to the strychnine it contains

Action and Result of Action.—Strychnine stimulates the central nervous system, particularly the spinal cord, increasing its reflex activity. It thereby increases motor activity and promotes all the physiologic functions which are reflex in nature, respiration, digestion, and nutrition. The effect on the respiratory center is only temporary. Strychnine has little direct action on the heart and in therapeutic doses does not affect the blood pressure.

Uses.—It has been widely used as an emergency respiratory and circulatory stimulant in shock, collapse and crises of pneumonia and other infections, but is now considered ineffective in this capacity.

1. It is employed as an antidote to central depressants such as chloroform and ether, and especially the barbiturates.

2. It has been thought valuable as a general muscular tonic because of the increased response to external stimuli which it causes. It is now believed that in the doses ordinarily employed the drug is ineffective for this purpose.*

*Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, The Macmillan Co., p. 262.

3. Strychnine in the form of Elixir of Iron, Quinine, and Strychnine is sometimes given as a bitter tonic to increase appetite and stimulate digestion. Strychnine has probably enjoyed an unwarranted popularity but because it has been used for a long time it continues to be used more or less.

Preparations and Doses:

Strychnine Sulfate, U. S. P. dose 2 mg. (gr. $\frac{1}{30}$)

Extract of Nux Vomica, N. F. dose 15 mg. (gr. $\frac{1}{4}$)

Tincture of Nux Vomica, N. F. dose 1.0 cc (m xv)

Elixir of Iron, Quinine, and Strychnine, N. F., dose 4 cc. (1 dram)

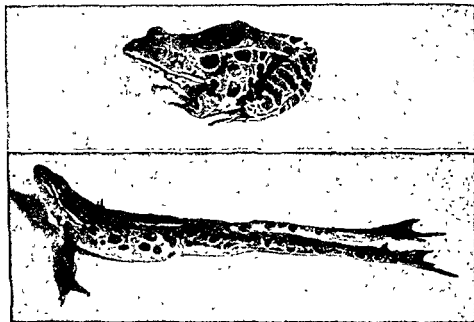


Fig. 14—Strychnine convulsion. Above, Normal frog. Below, Same frog in convulsion five minutes after the injection of 0.5 mg of strychnine sulfate hypodermically. Note marked extension of back and hind legs. All the muscles in the body are contracting, but the extensor muscles are stronger than the flexors. (From Gilbert and Moody: *Essentials of Pharmacology and Materia Medica for Nurses*, The C. V. Mosby Co.)

Administration.—For a rapid effect, strychnine is given hypodermically. The preparation for this purpose is the sulfate. The extract is usually given in the form of pills. The tincture has in the past been used as a tonic. The compound syrup contains gr. $\frac{1}{80}$ of strychnine in each dram: the elixir, gr. $\frac{1}{64}$ in each dram.

Poisoning.—Acute strychnine poisoning results from an overdose of the drug, taken by mistake or with suicidal intent. Strychnine

poisoning in children occurs occasionally due to their accidentally gaining access to some preparation containing strychnine. The symptoms occur within fifteen or twenty minutes after the drug has been taken and begin with a feeling of stiffness in the muscles of the face and neck, followed by twitchings of the face and limbs, and presently violent convulsions of the whole body, which occur at intervals varying from a few minutes to an hour. Between the attacks, there is usually complete relaxation of the muscles. Death may result during a convulsion from asphyxia due to spasm of the respiratory muscles, or during the period of relaxation from respiratory paralysis. The convulsions are due to excessive stimulation of the cord by strychnine. The patient is usually conscious to the end and suffers intense pain.

Treatment.—The main object in treatment is to prevent convulsions. It is advisable to postpone evacuation of the stomach and give a rapidly acting barbiturate, such as sodium amytal or sodium pentothal. Other central depressants may be used if barbiturates are not available; chloroform and ether may be used to control convulsions. If some of the drug is believed to be still in the stomach, gastric lavage may be performed. Potassium permanganate or tannic acid are effective antidotes. When the stomach has been emptied and the convulsions checked, chloral, bromides, or phenobarbital may be given repeatedly to prevent convulsions from returning. If the respiration fails at any time, artificial respiration and oxygen are administered.

During treatment the patient should be in a cool, darkened room, and should be protected from any sudden noise, jar, or change of any kind that would tend to bring on another spasm.

Strychnine is absorbed rapidly and excreted very slowly so that cumulative effects may occur which are similar to those of acute poisoning, such as nervousness, twitching of muscles of the face or extremities, diarrhea, and stiffness of the neck and jaw. If the drug is discontinued, the symptoms disappear.

It is worthy of note that strychnine is still found in a number of cathartic preparations and when taken in excess, as is likely to happen when children manage to get hold of a bottle of sugar-coated pills containing some of this drug, severe symptoms of poisoning may result. Nurses should inform mothers as well as other persons of the danger associated with the storage and administration of such preparations. Children have been killed as a result of such carelessness.

CONTRASTED ACTION AND EFFECTS OF CAFFEINE AND STRYCHNINE

1. Caffeine in small doses acts primarily on the cerebral cortex, in larger doses on the cortex, and in still larger doses probably on the spinal cord. In other words, it is a descending stimulant.

2. Strychnine affects the nervous system from below upward. Small doses affect the spinal cord, and larger doses affect the cord, the medulla, and finally the cortex.

3. Caffeine acts directly on voluntary muscle and on the tissues of the heart and kidneys, while strychnine acts upon these tissues indirectly.

4. The toxic effects of caffeine disappear rather quickly when the drug is discontinued, while the toxic effects of strychnine may prove grave and demand swift treatment.

Amphetamine (Benzedrine)

Benzedrine, a colorless liquid, is a synthetic preparation closely related to ephedrine and epinephrine and has a similar effect on the sympathetic nervous system. In addition, it is a potent stimulant of the central nervous system. Central effects of exhilaration, lessened fatigue, and talkativeness may follow doses of 10 to 20 mg. ($\frac{1}{3}$ - $\frac{1}{2}$ gr.). Its continued use may cause exhaustion, sleeplessness, dizziness, anorexia, and vomiting.

Therapeutic Uses.—Benzedrine Sulfate (Amphetamine Sulfate), N. N. R., is used for its central effects in the treatment of post-encephalitic Parkinson's disease, certain types of mental depression, narcolepsy, and for narcotic poisoning. Its use as a central nervous system stimulant is still in the experimental stage, and it may produce undesirable cardiac effects. It is contraindicated in those who suffer from cardiovascular disease. Use of Amphetamine Sulfate in the treatment of obesity is not an approved practice.*

Considerable danger lies in the promiscuous use of this drug to overcome sleepiness and to increase alertness, because of the danger of eliminating natural danger signs in the form of fatigue and because of the possibility of habit formation.

EMERGENCY STIMULANTS

As a rule, each hospital ward is supplied with a tray or container of so-called emergency drugs, some of which are certain to be central nervous system stimulants. Every nurse should know where such a tray is kept, what drugs are contained on it, and how to pre-

*N. N. R., 1947, p. 210.

pare them quickly and safely. Among the stimulants which the tray is likely to contain are:

1. Caffeine sodium benzoate
2. Camphor in oil
3. Coramine
4. Metrazol
5. Strychnine sulfate or hydrochloride
6. Atropine sulfate
7. Epinephrine
8. Aromatic spirits of ammonia

CENTRAL DEPRESSANTS

Depression or lessened activity of the central nervous system may result either from exhaustion due to overstimulation, or from the action of certain drugs administered for that effect. The state of mild depression is characterized by a lack of interest in surroundings, an inability to focus attention on any subject, and a lack of desire to move about or talk. The pulse and respiration are slower than normal; as depression progresses, all sensations of touch, sight, hearing, heat, cold, and pain are correspondingly lessened and motor and mental activities are decreased. If the depression is not checked, it progresses to unconsciousness, stupor, coma, and finally death from paralysis of the respiratory center.

The central depressants may be classified, according to their therapeutic use, in the following groups:

1. The analgesics, which relieve pain.
2. The hypnotics and sedatives, which induce sleep and rest.
3. The anesthetics, which produce loss of sensation.
4. The intoxicants.

I. ANALGESICS

The drugs which are used primarily for the relief of pain are opium and its derivatives, and the coal tar analgesics.

Opium is one of the oldest remedies known to man. It is described in Chinese literature written long before the time of Christ. The name comes from the Greek *opos*, juice.

Opium is the hardened dried juice of the unripe seed capsules of the *Papaver somniferum*, a species of poppy grown largely in China, India, Persia, and Asia Minor. The poppy plant is indigenous to Asia Minor, and from there knowledge of opium spread to Greece and

Arabia where physicians became well versed in its use. Arabian traders are responsible for its introduction into the Orient where it was known as "smoking dirt." The Chinese used it chiefly to control some of the symptoms of dysentery until its cultivation was exploited for commercial reasons by European powers and the opium habit spread through many parts of the Orient.

Paracelsus is credited with compounding the preparation "laudanum." Paregoric was first used as an elixir for asthma, and was prepared by a chemistry professor at Leyden. Thomas Dover, an English physician, used the powder as a sweating agent for gout in 1732.*

Opium in the crude form was used until well into the nineteenth century, before the chief alkaloid, morphine, was isolated. The discovery of other alkaloids soon followed and their use came to be preferred to that of the crude preparations.

Composition of Opium.—The active principles of opium are alkaloids of which there are some twenty in number although but three are used widely in the practice of medicine, namely,

Morphine
Codeine
Papaverine.

The alkaloids form twenty-five per cent of the active constituents of opium, the rest being made up of such things as gums, oils, resins, protein-like substances, etc. The natural alkaloids are divided into two chemical classes. Morphine and codeine fall into one class and papaverine into another. The two classes present different pharmacologic activities. Morphine and codeine act chiefly on the nervous system by a combination of depression and stimulation effects and by stimulation of smooth muscle. The other group, to which papaverine belongs, has little or no effect on the nervous system but a definite antispasmodic effect on smooth muscle.†

Heroin, dionine, and dilaudid are examples of synthetic alkaloids and therefore do not exhibit all or the same side effects as do the natural alkaloids. It is hoped that in time chemists will be able to make synthetic alkaloids which will have the specific advantages of the natural alkaloids without their disadvantages

Action and Result of Action.—The effects of opium are due chiefly to the morphine which it contains, hence the two drugs may be considered together.

*Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 186.

†Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 187.

A. *On the Cerebrum.*—Opium and morphine depress the cerebral cortex, especially the general sensory and psychic areas and also the optic thalami. Sensation and perception are dulled; a state of euphoria may result, prolonged concentration becomes difficult, anxiety and apprehension disappear, imagination is uninhibited and most important of all—*pain is relieved*. The smallest therapeutic dose results in the relief of pain in some instances without any other noticeable effects. The depression of cerebral centers which does not allow steady continuous stimuli to get through may also result in a compelling sleep which may last for several hours. Sudden, strong or intermittent stimuli, for some reason, do not appear to be blocked and the usefulness of this drug for certain kinds of pain is thus limited. Morphine, however, continues to be the most valuable analgesic in medicine, and ordinarily a nurse does not need to fear habit formation in a patient who is receiving the drug for severe pain. In fact, pain acts like an antidote for morphine and the dosage usually must be markedly increased if severe pain is to be controlled.

In small doses at least, morphine seems to have little or no effect on the motor areas of the brain.* The diminished restlessness is probably due to the fact that the brain is unable to respond to stimuli normally.

B. *On the Brain Stem and Hypothalamus.*—

1. The most dangerous action of morphine is its depression of the respiratory center in the medulla, resulting in slower and more shallow respirations.
2. Although opium and morphine in large doses may stimulate the vagus nerve and influence the rhythm of the heart, therapeutic amounts of these drugs have little or no effect on the blood pressure, heart rate or rhythm. The slowing in the pulse rate, which the nurse may sometimes observe in patients who receive morphine, is probably due to decreased restlessness and sleep.
3. The pupil-contracting center is stimulated. After moderate doses the pupils may be constricted and become "pin point" in size after toxic doses, enlarging again as the toxic state deepens.
4. The cough center is depressed and coughing is lessened.
5. The heat-regulating center is slightly depressed in therapeutic doses, resulting in slight reduction of temperature, although the decreased activity and increased perspiration may account for some change in temperature.

*Bastedo: *Materia Medica, Pharmacology and Therapeutics*, W. B. Saunders Co., p 447.



PLATE V.—*Papaver somniferum* (Opium Poppy). (From Jackson·
Experimental Pharmacology and Materia Medica)

6. The vomiting center may be stimulated which may be responsible for nausea and vomiting, although this reaction may be due to the formation of apomorphine.

C. *On the Spinal Cord*.—There is evidence that in laboratory animals morphine may cause sufficient stimulation of the spinal cord to produce convulsions. These have occasionally been observed in man when toxic doses have been taken and explains in part why morphine cannot be used for the treatment of strychnine poisoning.

D. *On the Cerebellum*.—Morphine seems to have a slightly depressant effect on the cerebellum to the extent that motor coordination is interfered with in a number of patients. Nurses will observe that patients sometimes have difficulty in handling a glass of water after receiving a hypodermic of morphine, or that they overreach or do not reach far enough when trying to get something from their bedside table. Patients who are given morphine before going to surgery may complain of dizziness and may stagger when they attempt to walk. Such difficulties must be foreseen by the nurse and a patient must never be allowed to walk unassisted.

E. *On the Peripheral Nerves*.—The sensory end organs and peripheral nerves are unaffected by morphine. The use of opium preparations for local effect is therefore an obsolete practice.* Opium preparations are absorbed from mucous membranes and when given as ointments or rectal suppositories act systemically.

F. *On the Gastrointestinal Tract*.—(Smooth muscle and glands).

1. Depression of glandular activity resulting in diminished secretion (all secretions are decreased except sweat which is increased).
2. Increased tone of sphincter muscles which produces delayed emptying of the stomach and small intestine.
3. Increased tone of the muscle of the stomach and intestine but decreased propulsive peristalsis. This often results in constipation. (The papaverine group of alkaloids produces relaxation of the gastrointestinal musculature.)
4. Depression of defecation reflex due to diminished sensitivity of the lining of the bowel and rectum.

Uses of Opium and Its Derivatives.—

A. The chief use of opium and morphine is to give relief in conditions of severe acute pain. They do this more efficiently than any

*Goodman and Gilman: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 192.

other known medicine. In surgical conditions in which the alleviation of severe pain may make diagnosis more difficult and lead to undue delay in operating, opium and morphine should not be used or they should be employed only in very small doses and with great caution. They should not be used in chronic conditions in which there is pain, as prolonged administration is almost certain to result in habit-formation. Exceptions to this rule are to be found in such conditions as inoperable cancer, etc., in which the patient cannot recover, and may be spared much unnecessary suffering by their use. Opium and morphine should not be used for the relief of pain in persons of neurotic or hysteric temperaments, unless their use is absolutely necessary. In general, they should not be used for the relief of pain when satisfactory results can be secured by the use of any other remedy.

B. Since the introduction of the coal tar analgesics and of hypnotics of the chloral group, opium and morphine are seldom used as pure hypnotics, but are extremely valuable in inducing sleep in sleeplessness due to violent pain or dyspnea.

C. To check peristalsis in such conditions as,

1. Peritonitis
2. Hemorrhage
3. Severe diarrhea
4. Operations on the stomach and bowel

Preparations of opium mixtures are more efficient than morphine for checking diarrhea because of their slow absorption and effect on smooth muscle.

D. As a preliminary medication for general anesthesia. Morphine is given frequently with atropine and is useful in promoting a relaxed state which favors a more satisfactory induction of the anesthetic. Atropine is frequently given with morphine to antagonize some of its untoward effects; e.g., atropine antagonizes the action of morphine on the respiratory center. Atropine has a greater value, however, in that it *checks secretions in the patient who has a general anesthetic*.

E. To quiet a nervous and overactive heart. To check pain in angina pectoris, and to relieve some forms of cardiac dyspnea.

F. To relieve cough. Codeine is the form most often given to depress the cough center.

G. In the treatment of peripheral or pulmonary embolism, for which papaverine has demonstrated therapeutic value.

Preparations and Dosage.—

Preparations of whole opium are given by mouth, and not parenterally.

Opium, U. S. P. Dosage: 0.06 Gm. (1 grain). ·

Powdered Opium, U. S. P. Dosage: 0.06 Gm. (1 grain); this dose contains about 0.006 Gm. ($\frac{1}{10}$ gr.) of morphine. Given orally.

Tincture of Opium (Laudanum), U. S. P. Dosage: 0.6 cc. (10 minims). Used to check intestinal peristalsis, and is given orally.

Camphorated Tincture of Opium (Paregoric), U. S. P. Dosage: 4 cc. (1 fluidram). This dose contains 0.0016 Gm. ($\frac{1}{40}$ grain) of morphine. It is a 1:250 solution of opium together with benzoic acid, camphor, oil of anise, glycerin, and diluted alcohol. Paregoric is used particularly to control intestinal peristalsis. Given orally.

Powder of Ipecac and Opium (Dover's Powder), N. F. Dosage: 0.3 Gm. (5 grains). Given orally. This has been used chiefly to break up a cold. It induces sweating and relieves the aches and pains which accompany a cold. It has, to some extent, been replaced by a combination of codeine and papaverine for the relief of a cold.

The alkaloids are usually prescribed in the form of their water-soluble salts, and are usually given parenterally, although they may be given by mouth.

Morphine Sulfate, U. S. P. Dosage: 10 mg. ($\frac{1}{6}$ grain), although the dosage varies from gr. $\frac{1}{8}$ to gr. $\frac{1}{4}$.

Morphine Hydrochloride, N. F. Dosage: 8 mg. ($\frac{1}{8}$ grain).

The action and uses of these two salts are the same. They may be given by mouth but are more frequently given by hypodermic injection. When given by mouth, they act in from ten to fifteen minutes; when given by hypodermic, in two to five minutes.

Codeine is available in the water-soluble salts, the most common being—

Codeine Sulfate, U. S. P., and *Codeine Phosphate*, U. S. P. The average dose is 30 mg. (gr. $\frac{1}{2}$). Codeine is methyl morphine. It is analgesic, hypnotic, and sedative. Its effects resemble those of morphine except that they are more feeble, and the sleep which it induces is not so deep or restful. Codeine is less constipating, less depressing to the respiration, and is not as habit-forming as morphine, although tolerance and addiction to codeine do occur. It is especially valuable to check a cough.

other known medicine. In surgical conditions in which the alleviation of severe pain may make diagnosis more difficult and lead to undue delay in operating, opium and morphine should not be used or they should be employed only in very small doses and with great caution. They should not be used in chronic conditions in which there is pain, as prolonged administration is almost certain to result in habit-formation. Exceptions to this rule are to be found in such conditions as inoperable cancer, etc., in which the patient cannot recover, and may be spared much unnecessary suffering by their use. Opium and morphine should not be used for the relief of pain in persons of neurotic or hysteric temperaments, unless their use is absolutely necessary. In general, they should not be used for the relief of pain when satisfactory results can be secured by the use of any other remedy.

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G. In the treatment of peripheral or pulmonary embolism, for which papaverine has demonstrated therapeutic value.

Idiosyncrasy.—Any unusual effect of opium or its derivatives other than the expected one is an idiosyncrasy. There may be:

a. *Idiosyncrasy of effect*, such as nausea and vomiting, excitement and restlessness instead of relaxation, tremors, delirium, insomnia, urticaria and skin rash, itching, and sneezing. (Infants are particularly susceptible to the depressant action of these drugs.) In some persons the nausea and vomiting are very pronounced after-effects of the drug, lasting, at times, for hours. It results usually as the effect of the drug is wearing off and is probably due to the formation of apomorphine.

b. *Idiosyncrasy of dosage*. Pronounced depression may sometimes be observed when moderate or small doses are given or, on the other hand, little or no effect may be secured with moderate or larger doses.

Symptoms of Poisoning; Treatment.—

a. **ACUTE POISONING.**—*Poisoning* with opium or morphine occurs from overdoses taken as a medicine or with suicidal intent. It has been stated that 40 per cent of all fatalities from poisoning have been due to these drugs. The symptoms begin with the usual depression which deepens into sleep, from which the person can at first be aroused only with great difficulty and later, not at all. The pupils become extremely constricted (pin-point pupils). *The respiration becomes shallow and slow*, sometimes as slow as three or four per minute. The heart is weakened and its rate is slowed as the toxic state deepens. Death results from failure of respiration. If opium has been taken, the odor may be detected in the breath. Morphine has no odor.

The treatment of morphine or opium poisoning is directed toward elimination of the poison from the body, guarding against failing respiration, and measures to sustain the patient. If the drug has been taken orally, the stomach should be emptied and lavaged with tannic acid (strong tea) or very dilute potassium permanganate solution (1:2000). Strong black coffee as hot as may be given safely may be administered by tube or orally, and also by rectum. Respiratory stimulants such as atropine, gr. $\frac{1}{100}$; caffeine with sodium benzoate, gr. $7\frac{1}{2}$, or ephedrin sulfate, gr. $\frac{3}{8}$, should also be given parenterally. If the breathing shows signs of failure, carbon dioxide and oxygen inhalations are a potent stimulant. Artificial respirations should be resorted to if the breathing shows signs of ceasing. If the patient has not gone into stupor every effort should be made to keep the patient awake and moving if at all possible. Additional measures consist of keeping the patient warm and dry

Pantopon is an artificial mixture, composed of the purified alkaloids of opium in the same proportion as they are found in opium, but in about five times the concentration. It is free from gums, resins, etc. Some think it is more valuable than opium itself. This is questionable. *Pantopon* has an advantage in that it can be injected and opium cannot. Patients who are sensitive to morphine can sometimes tolerate *pantopon* satisfactorily. The dosage is twice that of morphine. It may be administered orally or subcutaneously.

Papaverine Hydrochloride, U. S. P. Dosage, 0.1 Gm. ($1\frac{1}{2}$ gr.). Administered orally or intravenously it is used as an antispasmodic and does not interfere materially with the normal movements of the intestine. The effects on the brain are much less than those of morphine. *Papaverine* acts particularly on the smooth muscle of the body. The muscles which respond best to this alkaloid are those of the bronchi, gastrointestinal tract, blood vessels including the coronary arteries, the bile ducts, and the ureters.* Since *papaverine* is one of the alkaloids of opium, it comes under the Federal Narcotic Law although devoid of narcotic action. *Copavin* (Lilly) contains $\frac{1}{4}$ grain codeine sulfate, and *papaverine hydrochloride*, $\frac{1}{4}$ grain. It is an effective cough depressant.

Dihydromorphinone Hydrochloride (*Dilaudid Hydrochloride*), U. S. P., is prepared from morphine. The dose ($\frac{1}{24}$ - $\frac{1}{48}$ grain) is $\frac{1}{2}$ that of morphine and may be given orally, hypodermically, or by suppository. Side actions, such as nausea, vomiting, constipation, seem to occur less frequently than with morphine. Both addiction and tolerance to *dilaudid* occur, although it probably causes addiction less rapidly than morphine. Federal Narcotic regulations apply also to *dilaudid*.

Tolerance.—Different individuals require varying periods of time before the repeated administration of opium derivatives fails to have the effect which they originally produced. This condition is known as tolerance. A patient who suffers considerable pain may be relieved at first by a fourth of a grain of morphine but if the painful condition persists, the time will come when he requires an ever increasing size of dose to experience the same relief which he received in the beginning. Large doses may eventually be taken by the tolerant person which would have caused death if given as an initial dose. The mechanism of reaction in morphine tolerance is not definitely known.

*Goodman, L. and Gilman, A.: *The Pharmacological Basis of Therapeutics*. The Macmillan Co. P. 206.

must be rewritten at frequent intervals if the drug is to be continued. But even within such restrictions she should be alert to the possibilities of a growing dependence on a drug. On the other hand, she must not withhold opiates when their need is indicated. The situation of a postoperative patient with extensive surgery going through the first twenty-four hours after operation and that same patient five days later is quite different. Although p.r.n. orders may be left in both instances, the interpretation of the opiate needs for the patient should be quite different and requires the exercise of discriminating judgment on the part of the nurse. In the first situation there may be a need not only to control pain and general restlessness but also to prevent hemorrhage, stress and strain on sutures, etc. The physician has a right to expect that sufficient opiate be given to keep such conditions under control. In the second situation if the patient is convalescing satisfactorily, the free use of opiates instead of more mild sedatives or hypnotics may be laying an early basis for habit formation. It often means more work for the nurse to help a patient through a day or night without narcotics, but no nurse worthy of the name would hesitate at the course to be followed. The young or inexperienced student, who is puzzled about the best way to interpret orders, should never hesitate to consult her head nurse or supervisor.

Every nurse in the course of her life is likely to come in contact with one or more persons addicted to the use of drugs in some form. While a nurse needs to know what to look for and what to avoid doing, she should remember that the addict is just another sick individual, worthy of everything she can do to help him recover. Kindness, sympathy, gentleness, and firmness are essential attributes of a nurse no matter what a patient's psychologic or sociologic deficiencies may happen to be. The addict has learned to use a drug to help him bear things in his life which have become intolerable to him, therefore the treatment must go further and deeper than just breaking the physical dependence on the drug. There is need for psychiatric treatment which requires the aid of an expert.

Sad as it seems, addiction to drugs occurs among doctors and nurses in spite of their opportunity to become aware of the tragedy which lies in wait for the addict. Everything possible should be done to prevent the likelihood of people being tempted to use drugs inadvisedly. Once a nurse forms this habit she automatically puts herself out of her profession sooner or later, for no one can assume the responsibility of allowing her to care for helpless patients.

Harrison Narcotic Law, see Chapter XXIV, p. 519.

as possible and changing the patient's position frequently to prevent the development of hypostatic pneumonia. Prolonged stupor also requires that attention be given to food intake, fluids, and distention of the bladder. Measures should be avoided which uselessly exhaust the patient.

b. **CHRONIC POISONING.**—Frequent repeated doses of these drugs lead not only to marked tolerance, but also to a very strong desire for the drug which the victim seems powerless to resist. The results vary in different individuals, but in general, long-continued use leads to depression and weakness, not only of the body, but also of the mind and morals. The patient suffers a loss of appetite and various other digestive disturbances and soon becomes thin and anemic.

Later, he grows nervous and irritable, unable to work except under the influence of the drug, and he may engage in low moral practices. He seems particularly incapable of telling the truth and will resort to any method of obtaining the drug. Ill health, crime, degeneracy, and low standards of living are the result not of the effects of morphine itself but of the sacrifice of money, social position, food, and self-respect in order to get the daily dose of the drug.

Symptoms of addiction include constricted pupils, constipation or diarrhea, infections, scars, abscesses, especially on the anterior surfaces of the body, where a patient is able to give himself a hypodermic. When the drug is withheld the patient exhibits insomnia, yawning and sneezing, tremor, sweating, mental depression, muscular aches and pains, and numerous other symptoms both of organic and psychogenic origin. Codeine has less tendency to form the habit, but heroin (diacetylmorphine) is powerful in this respect and at present its manufacture is illegal, because it is so habit forming.

Treatment is best carried out in a sanitarium and consists in the administration of cathartics and sedatives, and the withdrawal of the drug. Many authorities now favor a rapid withdrawal. The Federal Government maintains two hospitals for the study and management of narcotic addicts under the United States Public Health Service. One is at Lexington, Kentucky, and the other is at Fort Worth, Texas.

It is generally agreed that the longer a patient has been addicted, the longer and the more difficult is the treatment.

Role and Responsibility of the Nurse.—Because addiction may have its origin in the use of opiates for the pain associated with disease processes, the nurse is a factor in the cause and prevention of drug addiction. She is protected by hospital rules and regulations because of the necessity of following written orders which

Toxic Symptoms.—Dizziness is the most common untoward effect, although dryness of the mouth, flushed face, increased perspiration, fall in blood pressure, slow pulse, and fainting are also reported. Nausea and vomiting are seen less frequently than with morphine. Withdrawal symptoms are found, especially in patients who have formerly been addicts, but it seems definitely less habit forming than morphine.

Effective beginning July 1, 1944, isonipecaïne or demerol was made subject to the provisions of the Harrison Narcotic Law.*

Analgesics and Antipyretics

During the latter part of the nineteenth century when chemists were trying to find a cheaper way of getting quinine than from the natural source, they discovered a number of compounds which differed in some respects from quinine but resembled it in their ability to reduce fever and relieve pain. Several of these compounds have survived chiefly because of their analgesic properties.

✓ THE SALICYLATES

Source.—The natural source of salicylic acid is willow bark, although it is now made synthetically from phenol. The cheaper synthetic product is as effective as the natural product. Salicylic acid itself is very irritating and can be used only externally, necessitating the synthesis of various derivatives for systemic uses. All these compounds will be referred to collectively as "salicylates" and will be discussed as a group. Usefulness of the various members of the group depends upon their solubility, salicylic acid content, and their ability to cause local irritation.

Action and Result of Action.—

A. Local Action.—Externally, salicylic acid is an irritant and destroys epithelial cells. It softens epidermis without producing inflammation. This action is made use of in the removal of warts, corns, fungous growths, and in the treatment of certain skin diseases. In solution the salicylates are weakly bacteriostatic and are capable of inhibiting certain fermentative and putrefactive processes. Methyl Salicylate produces irritation on both skin and mucous membrane and is used as a counterirritant. The irritant action on gastric mucosa is likely to cause epigastric distress, with resulting nausea and vomiting. It is thought, however, that gastric irritation may result from a central as well as a local action.

*J. A. M. A., 125: 914, 1944.

Merperidine Hydrochloride (Demerol Hydrochloride)

Demerol Hydrochloride is called a synthetic substitute for morphine. It is chemically related to atropine and is morphine-like in its depression of the central nervous system. Demerol hydrochloride has been included in the 1947 edition of N. N. R. It exhibits three main types of action:

1. *Analgesic*.—It exerts a strong analgesic action comparable to morphine, especially when given parenterally. Visceral pain is said to be relieved better than pain of the skeletal or neuromuscular systems* In man the analgesic effect appears to lie between that of morphine and codeine and lasts for five to six hours.†
2. *Spasmolytic*.—Demerol brings about relaxation of hypertonic muscle in a way similar to papaverine and atropine. It produces rapid relief of colicky pain and does not produce constipation, hence cannot replace the opiates in control of diarrhea. Relief of bronchial spasm has been observed, although the relief was not as rapid as that secured with epinephrine.*
3. *Sedative*.—Large therapeutic doses of demerol depress the central nervous system and produce sleep from which the patient is fairly easily aroused. It does not cause constriction of the pupil and does not depress the respiratory center. It seems to be a satisfactory preanesthetic drug.

Administration and Dosage.—Demerol is less powerful than morphine and its effects do not last as long. For the control of moderate pain 50 to 100 mg. ($\frac{3}{4}$ -1½ gr.) are given orally or parenterally every four hours. To control more severe pain 150-200 mg. (2¼-3 gr.) may be required. Repeated administration of these higher doses are contraindicated. Demerol may be given orally but better results seem to be obtained when it is given parenterally. Demerol is rapidly dissipated in the body and rapidly destroyed by the liver.

Uses.—1. As an analgesic which is less habit forming than morphine and, as a rule, does not affect respirations.

2. To relieve spasm of hypertonic muscle in the bronchial tubes, in the gastrointestinal tract, and in the ureters. It resembles atropine in its ability to check bronchial secretions

3. To compel sleep when insomnia is due to pain In obstetrics it may be used to lessen the severity of labor pains.

*Batterman and Himmelsbach: J. A. M. A. 122: 222, 1943.

†N. N. R., 1947, p. 28.

3. Sodium Salicylate is sometimes used as a sclerotic agent in the treatment of varicose veins.

B. Systemic Uses.—

1. The chief use of salicylates is in the treatment of acute rheumatic conditions and certain types of pain associated with muscles and joints. It is also given for various types of headache, painful menstruation, and neuralgias.

2. To produce antipyresis when reduction of fever brings a beneficial relief to the patient. Care must be exercised to avoid giving any of these preparations, however, if the patient is benefiting by the fever or if the course of the illness is obscured by the reduction in temperature.

3. Salicylates are sometimes used in the treatment of gout. They are less valuable for this purpose, however, than cinchophen.

4. Unpleasant symptoms associated with a cold or attack of influenza may be relieved by one or more of the salicylates since they may relieve the muscular aching, the headache, or fever, but their use should be accompanied by bed rest. They do not exert any effect on the progress of the infection. In other words, it is impossible to "break up" a cold with aspirin, as is rather popularly believed.

Preparations and Dosage.—

Acetylsalicylic Acid (Aspirin), U. S. P. Dosage: 0.3-1.0 Gm. (5-15 grains) every three or four hours as is necessary. Aspirin is relatively insoluble and hence less irritating to gastric mucosa. It has a rather bitter taste.

Sodium Salicylate, U. S. P. Dosage: 0.3-1.0 Gm. (5-15 grains) every three or four hours as needed. Relatively soluble in water. Has a sweet saline taste.

Both of above preparations may be given more intensively in acute rheumatic conditions, i.e., 1 gram every hour until toxic symptoms appear. Nausea can be controlled in part by simultaneous administration of soda bicarbonate in equal or double amounts of the dose. The route of administration is usually oral.

Methyl Salicylate (Oil of Wintergreen), U. S. P. Given chiefly in liniments and ointments. Too irritating to be given internally.

Salicylic Acid, U. S. P., is too irritating to be given orally but is a component of many ointments and preparations for external use.

B. Systemic Action.—The mechanism of analgesic action of the salicylates is not fully understood, but it is believed that they depress the optic thalami. Since analgesic doses do not produce dulling of consciousness, mental sluggishness, or disturbance of memory, the site of action is apparently not in the cortex. Relief of pain from the application of methyl salicylate is obtained by counter-irritation. Local application of powdered aspirin to relieve pain of a sore throat has no apparent basis in rational therapeutics.

The antipyretic action of these drugs appears to be accomplished by a resetting of the human thermostat for a normal temperature. A marked fall in temperature is produced in fever patients. Within the range of ordinary dosage the salicylates have no significant action on the heart and blood vessels. They do, however, bring about an increased excretion of uric acid, although the mechanism of action has not been proved.

The use of salicylates in the treatment of acute articular rheumatism and rheumatic fever approaches the role of a "specific." They bring about reduction of fever, pain, swelling, inflammation, and immobility of joints in a way which explains their major use. *They do not cure the disease or its complications* but they are of great value in controlling painful and disabling symptoms even though the effects may last only while the medication is continued. The relief seems to be accomplished only by antipyresis and analgesia, but the evidence is inconclusive as to whether these are the only actions.

Absorption.—Salicylates are rapidly absorbed from the stomach and duodenum and are rapidly excreted by way of the kidney, giving urine a greenish-brown color. Rapid excretion explains the need for large and frequent dosage. Salicylic acid, as well as methyl salicylate, is absorbed from the skin, but this route is too uncertain if systemic results are desired.

Therapeutic Uses.—

A. Local Uses.—

1. Salicylic acid is a constituent of corn and callus removers and is used to remove warts and upper layers of skin in some skin diseases. It is also used for fungous infections of the feet, a familiar preparation being Whitfield's ointment which contains benzoic acid and salicylic acid.

2. Methyl Salicylate is used as a counterirritant and is rubbed on and around painful joints. It is also used as a flavoring agent (Oil of Wintergreen).

3. Sodium Salicylate is sometimes used as a sclerotic agent in the treatment of varicose veins.

B. *Systemic Uses.*—

1. The chief use of salicylates is in the treatment of acute rheumatic conditions and certain types of pain associated with muscles and joints. It is also given for various types of headache, painful menstruation, and neuralgias.

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Methyl Salicylate (Oil of Wintergreen), U. S. P. Given chiefly in liniments and ointments. Too irritating to be given internally.

Salicylic Acid, U. S. P., is too irritating to be given orally but is a component of many ointments and preparations for external use.

Toxicology and Treatment.—The safety range of the salicylates is a wide one, and most cases of poisoning are mild. However, the indiscriminate use of these drugs by lay people for every sort of ache and pain has resulted in numerous instances of toxic reactions. Mild poisoning is called salicylism and consists of ringing in the ears, dizziness, disturbance of hearing and vision, sweating, nausea, and vomiting and diarrhea. The so-called salicylic jag results from stimulation of the central nervous system and may progress to a delirious state. Skin eruptions have also been reported. Deaths from salicylate poisoning have been reported. Methyl Salicylate in doses as small as 6 cc. has caused death in children. More dangerous symptoms include depression, coma, circulatory collapse, and respiratory failure. Poisoning and untoward reactions to the salicylates are frequently a matter of personal idiosyncrasy.

The treatment of poisoning is largely symptomatic. All that is usually necessary is to stop the drug and give plenty of fluids. If excessive doses have been taken, it may be necessary and advisable to wash the stomach and instill a saline evacuant. If the symptoms are those of depression, give stimulants; if the symptoms are those of overstimulation, give mild sedatives.

Cinchophen

Cinchophen, N. F., was introduced into medicine under the name of atophan. It is a synthetic preparation which occurs as a white powder having a bitter taste. It is similar in action to sodium salicylate, but is more prompt and powerful. The effects of cinchophen last only while the administration of the drug continues. It is an exceptionally efficient analgesic in gout and acute and chronic arthritis and similar conditions. In gout it is thought that the cinchophen drugs increase the permeability of the kidney to uric acid and its salts. In acute gouty attacks, suitable doses of cinchophen relieve the pains around the joints very promptly and without undesirable side actions. Excessive doses, however, result in various symptoms of poisoning, among which are gastric distress with acid eructation, and diarrhea. These symptoms can be avoided by giving with it small doses of sodium bicarbonate. Cinchophen sometimes induces a scarlet and urticaria-like rash or a rash with vesicles, and occasionally causes cardiac distress with dizziness. *Excessive doses or the long-continued use of moderate amounts may cause damage to the kidney and liver. The appearance of skin rash, vomiting, heartburn, diarrhea, or jaundice are danger signals and demand that the drug*

be discontinued at once. Relatively small doses occasionally induce symptoms in patients showing idiosyncrasy. Special caution is necessary in the use of cinchophen if the patient is known to have kidney disease. For this reason the indiscriminate use of cinchophen for the relief of pain is extremely dangerous. In fact, its use is not recommended except for severe pain which does not yield to safer remedies.*

Cinchophen may be prescribed in quantities varying from 0.5 Gm. (8 grains) four times a day to 1 Gm. (15 grains) three times a day. The drug should always be taken with large quantities of water. Some authorities recommend the administration of sodium bicarbonate along with the cinchophen to prevent free precipitation of uric acid in the urine.

Neocinchophen

Neocinchophen, U. S. P., has the same action and uses and dosage as cinchophen but has the advantage of being almost devoid of taste, and much less irritating to the stomach and kidneys. Because several cases of atrophy of the liver have followed the use of these drugs, their use has been much decreased. The majority of patients, however, do not show evidence of toxic reaction even after prolonged medication, and many patients receive great relief.

The average dosage is 0.3 Gm. (5 grains).

Colchicine

Colchicine is an alkaloid obtained from the seeds of *Colchicum* (Meadow saffron) which produces effective results in the treatment of acute gout. Its systemic action is that of antirheumatic and analgesic but locally it is an irritant. The mechanism of its systemic action is unknown. It does not have any effect on uric acid metabolism and does not relieve pain other than that associated with acute gout.

Symptoms of Poisoning.—Colchicine is a violent poison. Overdoses produce nausea and vomiting, severe diarrhea, violent abdominal cramps, shock, and hematuria. The pulse may become rapid and thready, the respirations slow, and death may result from respiratory failure. Its use in spite of its toxic effects is justified on the basis that some patients with gout are afforded dramatic relief.

Treatment.—Wash out the stomach with tannic acid solution and follow with a saline cathartic. Demulcent drinks may be given to soothe the irritated gastrointestinal tract. Keep the patient warm.

*N. N. R., 1947, p. 26.

Morphine and atropine may be given to relieve pain and caffeine to stimulate respiration.

Preparations and Dosage.—

Tincture of Colchicum Seed, U. S. P. Dosage: 2 cc. (minims, 30).
Colchicine, U. S. P. Dosage: 0.5 mgm. ($\frac{1}{120}$ grain).

Colchicine in tablet form is the preparation usually preferred. It is given by mouth and repeated every two or three hours. It should be discontinued when the patient's pain had been relieved or if toxic symptoms appear; e.g., doctors sometimes order colchicine to be given until the patient begins to have diarrhea.

OTHER COAL TAR ANALGESICS

Acetanilid and phenacetin are sometimes called para-aminophenol derivatives, and it is probable that they exert their typical action in the body after changing to para-aminophenol. Antipyrine and aminopyrine are phenyl-pyrazolone derivatives, and their action is much the same as phenacetin except in the type of poisoning which they produce.

Action and Result of Action.—The coal tar products are absorbed in from 25 to 30 minutes, and after absorption act chiefly to depress the brain and the heat-regulating center. There is little or no effect on a normal temperature, but in febrile patients they cause a decided drop in temperature accompanied by profuse sweating. The depressant action on the brain is probably centered largely in the basal ganglia since there is no decrease in intellectual activities. The most prominent result of this action is the relief of certain types of pain associated with arthritis, rheumatism, neuralgias, etc. A combination of the different drug groups is sometimes more effective than any one alone. They are the active ingredients of many headache powders. Ordinary therapeutic doses have no important cardiovascular actions although excessive doses may act as cardiac depressants, and they should be used with caution in patients with heart disease or in those who exhibit any unusual reactions to the drugs. Indiscriminate use of the coal tar analgesics may result in serious consequences.

Administration.—The coal tar analgesics are best given orally in the form of powders, cachets or capsules; if tablets are used, they may be crushed before swallowing. Caffeine is sometimes added to preparations of these drugs on the supposition that it will help to improve circulation.

Sodium bicarbonate in twice the amount of the analgesic helps to prevent nausea. Since untoward results sometimes occur even with

small doses, it is advisable to begin with the minimum amount of each drug and repeat with caution. When small doses do not produce the desired effect, larger doses are likely to fail also, and some other remedy is indicated. Acetanilid is considered the most dangerous drug of the group, but it does not deserve this reputation which was gained by giving too large doses. The initial dose should be 0.2 Gm. (3 grains) to be repeated in three hours. Phenacetin may wisely be started with 0.2 Gm. (3 grains).

Preparations and Dosages.—

Acetanilid, U. S. P. Dosage: 0.2 Gm. (3 grains).

Phenacetin (Acetophenetidin), U. S. P. Dosage: 0.3 Gm. (5 grains).

Antipyrine, N. F. Dosage: 0.3 Gm. (5 grains).

Aminopyrine, U. S. P. (Pyramidon). Dosage: 0.3 Gm. (5 grains).

Poisoning may occur from a single overdose, but is usually the result of the prolonged use of some proprietary headache remedy. The symptoms are profuse sweating, nausea and vomiting, skin eruptions, weakness, cyanosis and a slow, weak pulse and respiration. More severe cases show subnormal temperature, lowered white cell count, and collapse. Aminopyrine seems to be a particularly bad offender in the production of granulocytopenia and should not be administered without frequent leucocyte counts at regular intervals. It is frequently compounded in proprietary remedies with other drugs. Veramon is pyramidon and veronal; cibalgin is pyramidon and dial. Acetanilid and Acetophenetidin are often found in headache and pain-killing medicines and poisoning most often occurs from lay use of patent medicines of this type.

Treatment.—In mild cases, it is sufficient to stop the drug. In more severe cases, wash out the stomach and keep the patient warm and quiet in bed, and give atropine and other stimulants.

Habit Formation.—The relief from headache and nervousness which these drugs give is only temporary, so that the temptation to repeat the dose is strong and a habit may be formed. The drugs in themselves are probably not habit forming, but the persistence of pain, if the cause is not removed, may cause habit formation to develop. Their prolonged use should not be encouraged because, aside from the danger of poisoning, continued use may cause various digestive disturbances, increased nervousness and sleeplessness.

Uses.—

1. As *analgesics* for headache, and for pain associated with rheumatism, arthritis, dysmenorrhea, toothache, nervous excitability, etc

They help to relieve the numerous aches and pains which accompany colds and influenza, tonsillitis, etc. Their use in the mentioned conditions is ordinarily preferable to morphine.

Acetanilid, phenacetin, antipyrine, and aminopyrine are used mainly for headaches. Headache in many instances is one of the least understood problems in medicine. The term *headache* should be limited to pain within the skull.

Relatively little is known concerning the cause of headache, hence an explanation of how these drugs relieve the pain is uncertain. Some headaches may be due to a rise in the pressure of the cerebrospinal fluid. In such cases, analgesics may cause relief by causing a general movement of the water from the tissues into the blood. The forms of headache due to migraine and eye strain may be due to spasmodic contraction of the cerebral vessels. Some headaches may be due to an upset of the sympathetic nervous system. There are other conjectures and theories. Since we often do not know the pathology, it is impossible to offer an adequate explanation for the action of analgesics.

2. *As Antipyretics.*—This use is secondary to that of analgesia, but some of these drugs are still given to reduce temperature as well as to relieve pain. Persons should be advised to go to bed after taking these drugs, especially in case of a cold, influenza or the "grippe." More harm than good may result if the patient becomes chilled during the antipyretic and diaphoretic actions of these preparations.

II. HYPNOTICS AND SEDATIVES

A hypnotic is a drug which produces sleep, and as a class of drugs has a wide use, especially in hospitals where many factors operate to make sleep difficult or sometimes impossible. When we consider the number of people on a hospital ward, some of whom must be more or less constantly active, and the noise which results from their activity, the unfamiliar surroundings for the patients, different kinds of beds from which the patients may be accustomed, physical discomforts, and the hundred and one ways in which the hospital differs from the patient's home, it is no wonder that many patients have difficulty in getting a restful sleep.

Good nursing will take into consideration the natural factors which are responsible for sleep and will seek to provide such conditions as will favor them:

- a. Decreased external stimuli to which the nervous system may respond.

- b. Decreased intellectual activities.
- c. Diminished blood supply to the brain.

Noise, especially persistent noise, such as comes from dripping faucets and flapping window shades as well as loud speaking, slamming of doors, intermittent muffled laughter, rattling carts, etc., has no place where sick people are trying to sleep. It would be well for every nurse to go at some time or other, to a vacant room, sit down and analyze the noise which comes from the ward. She will be surprised at the amount, variety, and needlessness of much of it.

Equally important is the elimination of annoying body discomforts, such as cold feet, an aching back, a wrinkled bed, too many or too few pillows or blankets, poor ventilation of the room, a distended bladder or bowel, or hunger of the patient. It is a poor nurse who will attempt to relieve such discomforts with a hypnotic. The fact that a drug is specifically ordered for the patient to provide sleep does not presuppose that the essentials of good nursing will be neglected.

In the same way that physical discomforts may prevent sleep, numerous and sometimes petty worries may persist in the patient's mind until they assume mountainous proportions. It may be that a patient cannot sleep because he is convinced that he cannot, and such a state of mind may actually prevent sleep. Patients can sometimes be reassured that if they can get adequate rest, they will get along very well, since in their inactive state they do not require as much sleep. An alert nurse will recognize these states of mind and will seek to find a way to relieve the worried state or try to establish a more satisfactory pattern of thought.

Characteristics of a Satisfactory Hypnotic.—Because it is imperative that patients with certain types of illness secure sleep in order to recover, it is desirable that the hypnotic that is chosen will produce sleep that is as nearly like that of natural sleep as possible. The hypnotic should (1) act within a reasonable length of time, (2) produce a restful uneventful sleep, (3) allow the patient to awaken somewhere near his usual awakening hour, (4) and should produce no undesirable "hang-over" effects the next day.

Terminology.—The terms hypnotic, somnifacient, soporific, and narcotic are synonymous in meaning, referring to the production of sleep. A sedative has a quieting effect on the body, or promotes a state of relaxation and rest not necessarily accompanied by sleep. Hypnotics and sedatives are not necessarily different drugs; a small dose of a drug may act as a sedative while a larger dose of the same drug may act as a hypnotic.

Classification of Hypnotics and Sedatives (for convenience of study).—

1. Barbiturates
2. The Sulfone Group of Hypnotics
3. The Chlorinated Hypnotics and Paraldehyde
4. Bromides

1. The Barbiturates

History.—Barbital was introduced by Emil Fischer and von Mehring in 1903 under the trade name of veronal. It has survived years of clinical use and is still a useful hypnotic. Phenobarbital is the second oldest of the barbiturates and is also known as luminal. Since its introduction, many other barbiturates have been synthesized whose clinical values have not always been clearly established. However, slight changes in the molecular make-up of individual members are responsible for compounds which exhibit interesting properties and special uses.

Physical Properties.—The barbiturates are all colorless white crystalline powders which have a slightly bitter taste and are slightly soluble in water and freely soluble in alcohol.

Pharmacologic Action.—a. The main action appears to be that of depression of cells in the brain stem and basal ganglia. The extent of action varies from a mild sedation to a deep anesthesia, depending upon the drug used, the method of administration, the dosage, and also the reaction of the individual's nervous system. The barbiturates are not analgesic and cannot be depended upon to produce sleep when insomnia is due to pain.* However, when combined with an analgesic the sedative action seems to re-enforce that of the analgesic. Therapeutic doses of the longer acting barbiturates may result in depression of spirits and lowered vitality on the day following administration. Many of the barbiturates, however, produce a dreamless sleep from which the patient awakens refreshed.

b. All of the barbiturates depress the motor areas of the brain when given in large doses but phenobarbital exerts a selective action on the motor cortex even in small doses. This action promotes a state of muscular relaxation.

c. Hypnotic doses of the barbiturates do not appreciably affect the heart and respiratory centers of the medulla. However, large or toxic doses definitely depress these centers to the end that death is usually due to respiratory failure.

*Goodman and Gilman: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 131.

Therapeutic Uses.—

1. *As hypnotics.*—For best effects the barbiturates should be administered at such a time as will coincide with the usual time of retirement. Long- or short-acting members should be chosen in accordance with the patient's needs and type of insomnia.

2. *As sedatives.*—The barbiturates have, for the purpose of sedation, a wide range of therapeutic use. Sedation can be obtained in a relatively short time and barbiturates are used for a variety of anxiety and nervous tension states.

3. *As anticonvulsants.*—Barbiturates are used to prevent or control convulsive seizures associated with tetanus, epilepsy, cerebral pathology, and strychnine poisoning. Phenobarbital has proved itself especially valuable in the prevention and control of grand mal seizures of epilepsy.

4. *To produce anesthesia.*—For selected forms of surgical procedures of brief duration, rapid-acting forms of barbiturates have been employed.

Evipal sodium and pentothal sodium, N. N. R., are used intravenously as quick-acting general anesthetics, with an early recovery period. It should be emphasized that the intravenous use of barbiturates may be a valuable procedure, but such use is potentially dangerous and should be administered by anesthesia experts, and for short operations.

5. *As preanesthetic medications.*—This may be in the form of a long-acting barbiturate given the night before operation or given a few hours before general anesthesia. The drug is usually given by mouth and in a dosage somewhat greater than that given for hypnotic effect only.

Administration.—Preparations of the barbiturates are given in the form of powders, tablets, solutions, capsules, and suppositories. Tablets should be crushed and if mixed with a medium such as hot milk, care should be taken that the mixture is well stirred and that the patient gets all of the medication. Many of these drugs are given by mouth, although they may be given by hypodermic injection intravenously or by rectum. The intravenous route is the most dangerous one. It should not be attempted except by experts for short operations. The highly soluble sodium salts are the preparations chosen for parenteral medication. Sedative doses are smaller than those given for hypnotic effect and are administered several times during the course of the day.

Idiosyncrasy.—Unusual effects or reaction to this group of drugs may be exhibited as one or more of the following:

1. Marked symptoms of "hang-over": listlessness prolonged depression, nausea, emotional disturbances.
2. Skin rash, urticaria, swelling of the face, asthmatic attack.
3. Bad dreams, restlessness, delirium.

Preparations and Dosage.—

TABLE I

PREPARATION	USUAL ADULT DOSAGE	USUAL METHOD ADMINISTRATION	LENGTH OF ACTION
* 1. Barbitol, U. S. P. (Veronal)	0.3-0.5 Gm. (5-10 grains)	Orally	Long acting
* 2. Phenobarbital, U. S. P. (Luminal)	0.030-0.090 Gm. ($\frac{1}{2}$ -1 $\frac{1}{2}$ grains)	Orally	Long acting
3. Pentobarbital Sodium, U. S. P. (Nembutal)	0.1-0.2 Gm. ($\frac{1}{2}$ -3 grains)	Orally; rectally	Moderately long acting
* 4. Amytal, N. N. R.	0.1-0.3 Gm. ($\frac{1}{2}$ -5 grains)	Orally	Moderately long acting
5. Seconal Sodium, N. N. R.	0.1-0.2 Gm. ($\frac{1}{2}$ -3 grains)	Orally; rectally	Short acting
6. Evipal Sodium, N. N. R.	2-4 cc. 10% sol.	Intravenously	Short acting
7. Pentothal Sodium, N. N. R.	2-3 cc. 5% sol.	Intravenously	Short acting
* 8. Alurate, N. N. R.	0.065-0.13 Gm. (1-2 grains)	Orally	Long acting
9. Dial, N. N. R.	0.1-0.3 Gm. ($\frac{1}{2}$ -5 grains)	Orally	Long acting
* 10. Ipral Calcium, N. N. R.	0.12-0.25 Gm. (2-4 grains)	Orally	Long acting
11. Neonol, N. N. R.	0.05-0.4 Gm. ($\frac{1}{4}$ -6 grains)	Orally	Long acting
12. Phanodorn, N. N. R. (Cyclobarbitol)	0.1-0.4 Gm. ($\frac{1}{2}$ -6 grains)	Orally	Moderately long acting
* 13. Pernoston, N. N. R.	0.2 Gm. (3 grains)	Orally	Moderately long acting
14. Sandoptal, N. N. R.	0.2-0.8 Gm. (3-12 grains)	Orally	Moderately long acting

*Sodium salts are available.

• Symptoms and Signs of Poisoning.—

A. ACUTE.—The general toxic reactions to the barbiturates are essentially similar. They are lethargy, stupor, coma, muscular relaxation, slow and shallow respirations, hypotension, tachycardia, and subnormal temperature which may be followed by fever. In fatal cases the terminal event is usually a bronchial pneumonia or pulmonary edema, accompanied by high fever and pulse rate. The therapeutic range of dosage is greatest with barbitol. Death has followed less than 1 Gm. (15 gr.), but recovery has occurred after taking 18 Gm.

(McNally). Five grams in all cases will produce alarming symptoms. Any dose above the therapeutic dose should be considered dangerous.

Treatment of Poisoning.—The treatment of poisoning consists in a prompt lavage of the stomach and stimulation of respiration with drugs, such as aromatic spirits of ammonia, picrotoxin, strychnine, coramine or caffeine sodium benzoate. Coffee enemas may also prove useful as well as the use of sodium bicarbonate to protect against acidosis. Additional treatment might include the use of oxygen and carbon dioxide for the respiratory condition, the administration of fluids and the application of external heat.

B. CHRONIC.—Barbiturate habituation and addiction is not infrequent, especially among drug addicts who have difficulty in getting opiates. Symptoms of chronic poisoning may consist of slowness of thought, mental depression, incoherent speech, failing memory, skin rash, weight loss, gastrointestinal upsets and anemia. There is frequently an ataxic gait and some mental confusion. Treatment consists in stopping all forms of the drug, promoting elimination, and general supportive therapy. Best results are probably obtained in an institution and even then there is a rather high percentage of failures.

Legislation.—These drugs in the past have had a wide use and have been easy to get which resulted in indiscriminate use and use for suicidal purposes. At present many states have passed legislation patterned after the Harrison Narcotic Act which restricts the sale of hypnotic drugs and prohibits the sale or possession of barbiturates except under proper licensure. Barbiturates may not be purchased or dispensed without a physician's prescription and the prescription may not be refilled without the physician's written sanction.

Diphenylhydantoin Sodium, U. S. P. (Dilantin Sodium)

Dilantin is related chemically to the barbiturates. It is an odorless, white or cream-colored powder, with a bitter taste. It is an anticonvulsant and has been found very efficient in the treatment of epilepsy. It is more effective in controlling seizures of the grand mal type, than those of the petit mal. It does not cure mental defects or the mental deterioration found in the epileptic. Its hypnotic action is relatively weak. Various untoward actions have been observed during its use. These include dry skin, dermatitis, itching, tremors, dizziness, nausea, vomiting, fever, apathy, difficult breathing, and hallucinations. Scurvylike symptoms of the gums have been observed, but its use does not interfere with the utilization of vitamin C. The significance of these reactions is not fully known. Dilantin is strongly alkaline and may cause gastric irritation.

Idiosyncrasy.—Unusual effects or reaction to this group of drugs may be exhibited as one or more of the following:

1. Marked symptoms of "hang-over": listlessness prolonged depression, nausea, emotional disturbances.
2. Skin rash, urticaria, swelling of the face, asthmatic attack.
3. Bad dreams, restlessness, delirium.

Preparations and Dosage.—

TABLE I

PREPARATION	USUAL ADULT DOSAGE	USUAL METHOD ADMINISTRATION	LENGTH OF ACTION
* 1. Barbitol, U. S. P. (Veronal)	0.3-0.5 Gm. (5-10 grains)	Orally	Long acting
* 2. Phenobarbital, U. S. P. (Luminal)	0.030-0.090 Gm. (½-1½ grains)	Orally	Long acting
3. Pentobarbital Sodium, U. S. P. (Nembutal)	0.1-0.2 Gm. (1½-3 grains)	Orally; rectally	Moderately long acting
* 4. Amytal, N. N. R.	0.1-0.3 Gm. (1½-5 grains)	Orally	Moderately long acting
5. Seconal Sodium, N. N. R.	0.1-0.2 Gm. (1½-3 grains)	Orally; rectally	Short acting
6. Evipal Sodium, N. N. R.	2-4 cc. 10% sol.	Intravenously	Short acting
7. Pentothal Sodium, N. N. R.	2-3 cc. 5% sol.	Intravenously	Short acting
* 8. Alurate, N. N. R.	0.065-0.13 Gm. (1-2 grains)	Orally	Long acting
9. Dial, N. N. R.	0.1-0.3 Gm. (1½-5 grains)	Orally	Long acting
* 10. Ipral Calcium, N. N. R.	0.12-0.25 Gm. (2-4 grains)	Orally	Long acting
11. Neonol, N. N. R.	0.05-0.4 Gm. (¾-6 grains)	Orally	Long acting
12. Phanodorn, N. N. R. (Cyclobarbitol)	0.1-0.4 Gm. (1½-6 grains)	Orally	Moderately long acting
* 13. Pernoston, N. N. R.	0.2 Gm. (3 grains)	Orally	Moderately long acting
14. Sandoptal, N. N. R.	0.2-0.8 Gm. (3-12 grains)	Orally	Moderately long acting

*Sodium salts are available

Symptoms and Signs of Poisoning.—

A. ACUTE.—The general toxic reactions to the barbiturates are essentially similar. They are lethargy, stupor, coma, muscular relaxation, slow and shallow respirations, hypotension, tachycardia, and subnormal temperature which may be followed by fever. In fatal cases the terminal event is usually a bronchial pneumonia or pulmonary edema, accompanied by high fever and pulse rate. The therapeutic range of dosage is greatest with barbitol. Death has followed less than 1 Gm. (15 gr.), but recovery has occurred after taking 18 Gm.

While therapeutic doses do not produce untoward actions on respiration and circulation, large doses produce severe poisoning, and prolonged usage brings about cumulative effects.

Symptoms of poisoning include confusion, ataxia, gastrointestinal upsets, pink or red colored urine, and albuminuria.

Preparations and Dosage.—

Sulfonmethane, N. F. (Sulfonal). Dosage: 0.75 Gm. (12 grains).

Sulfonethylmethane, N. F. (Trional). Dosage: 0.75 Gm. (12 grains).

These preparations are given orally in hot water or milk several hours before sleep is desired.

3. The Chlorinated Hypnotics and Paraldehyde

A. Chloral Hydrate.—Chloral hydrate is the oldest member of the hypnotic group and is still in use today. It is a hydrate of trichloraldehyde. It is a crystalline drug which has a bitter caustic taste and penetrating odor. It is incompatible with strong alkalis, breaking down and liberating chloroform but in the body tissues and tissue fluids, remains stable.

Action of Chloral Hydrate.—1. It depresses the cerebrum and to some extent the spinal reflexes. Sleep occurs in a relatively short time and will last from five to eight hours. The sleep greatly resembles that of natural sleep; the patient can be awakened without difficulty. There is little or no analgesic effect.

In therapeutic doses there is little or no effect on the heart and respiratory center. The pulse and blood pressure are not lowered more than can be observed in ordinary sleep. In large doses chloral hydrate depresses the respiratory and vasomotor centers, resulting in slowed respiration and dilation of cutaneous blood vessels. The effect on the heart is similar to that of chloroform.

Uses.—

1. *As a sedative.*—For sedation, chloral hydrate is similar to paraldehyde and the barbiturates. It is sometimes used in the treatment of withdrawal symptoms of drug addiction and in chronic alcoholism.

2. *As a hypnotic* when insomnia is not due to pain.

Chloral hydrate is contraindicated in patients with liver and heart disease or in cases of severe gastritis.

Preparations; Dosage and Administration.—

The adult dose of chloral hydrate, U. S. P., is 0.6 Gm. (10 grains) although larger doses are sometimes given. Because the drug is irritating to mucous membranes it should be given well diluted

Dosage.—The dose varies with the patient, and some untoward actions may arise. Mild symptoms do not require that the dosage be stopped. The beginning daily dose for adults is 0.1 Gm. ($1\frac{1}{2}$ gr.) in half a glass of water three times daily. If necessary, this dose may be doubled. Children over six years old may be given the adult dose three times a day for one week; after which, if necessary, it may be increased to four doses per day. The dose should be lessened for children under this age. Increase in dosage should be made slowly and under careful observation. The transition from phenobarbital, bromides, and other hypnotics should be made gradually and with some overlapping of dosages. The drug is more effective and useful for the younger patients and for those in good physical condition. Dilantin is available in capsules containing from 0.03 Gm. to 0.1 Gm. ($\frac{1}{2}$ to $1\frac{1}{2}$ gr.). It is more rapidly effective if given before meals, but if gastric distress is caused it should be given immediately after meals.

2. The Sulfone Group of Hypnotics

Trimethadione, N. N. R. (Tridione)

Trimethadione is an anticonvulsant used principally in the treatment of petit mal epilepsy. It is not effective for treatment of grand mal seizures. It may sometimes be given along with diphenylhydantoin sodium when the latter alone is not effective. The drug appears to be somewhat more effective in children than in adults.

Symptoms of toxicity appear rather infrequently. Gastric irritation, nausea, skin eruption, and blurring of vision are considered indications for reduction of dosage or temporary withdrawal of the medication. Careful medical supervision of patients receiving the drug is essential. Rare cases of aplastic anemia indicate a need for careful and periodic blood examinations.

The drug is contraindicated in patients with liver or kidney damage or in those with disease of the optic nerve.

Administration and Dosage.—

Trimethadione is usually given by mouth in 0.3 Gm. capsules. The dosage may vary from 1 to 2 Gm. a day given in divided doses. Optimum dosage for each patient must be determined individually.

Two members of this group of hypnotics have been used in therapeutics. One is Sulfonmethane, N. F. (Sulfonal), and the other is Sulfonethylmethane, N. F. (Trional); the latter is the drug of preference. Their use is limited because they are slowly absorbed and their hypnotic effects are often delayed for several hours. Sulfonethylmethane produces the more rapid effects of the two.

Absorption and Excretion.—Paraldehyde is rapidly absorbed from all mucous membranes and is excreted in the expired air a short time after administration. The odor and taste of the drug may be especially objectionable to the patient.

Preparation and Dosage:

Paraldehyde, U. S. P. The dose is 3-8 cc. up to 15 cc. given by mouth or rectally. It may be disguised in a suitable medium, such as a syrup, when given by mouth or in a thin oil for rectal administration.

Uses.—Paraldehyde is employed largely for its hypnotic and sedative effects in delirium tremens, nervous disorders, and sometimes as a preanesthetic medication. Although its chief disadvantage is its odor and taste, it is one of the least toxic hypnotics.*

4. The Bromides

A. History.—Bromide was discovered in the waters of the Mediterranean in 1826 by Balard. In 1864 potassium bromide was used by Behrend in certain cases of sleeplessness and a little later by Vigouroux and Voisin in epilepsy. It was assumed that its action was similar to that of potassium iodide, and it was given in large doses (30 grams per day) for glandular swellings of syphilis and tuberculosis. These large doses revealed its peculiar narcotic or sedative action which at present is the most important action.

B. Physical Properties.—The bromides are white crystalline substances which are odorless and have a pungent saline taste. They are readily soluble in water.

C. Pharmacologic Action.—

1. *Nervous System.*—Bromides are given mainly for their depressant action on the central nervous system. The depression may vary from a mild sedation to a deep coma, depending upon dosage given. Bromides are not directly hypnotic in the same way that morphine and chloral hydrate are but favor sleep by depressing the centers, which prevent orderly impressions from exerting a disturbing influence. The entire cerebrospinal axis, with the exception of the medulla, is readily affected. Large therapeutic doses depress the psychic centers, motor areas, and many of the reflexes of the brain and spinal cord. The sensory areas concerned with pain, as well as the respiratory center, are not much affected except by very large doses. The irritability of the cough center is lessened, and coughing may

*Goodman and Gilman. The Pharmacological Basis of Therapeutics, The Macmillan Co., p 180

in a syrup, starch suspension, or in water or milk. It should not be given in any alcoholic medium. It is too irritating to be given by hypodermic but may be given rectally if mixed with a bland oil or cooked starch mixture.

The nurse should be on the alert for untoward reactions in patients who are given chloral hydrate. A rather frequent check on the pulse and blood pressure will help her to detect signs of undesirable reaction. If symptoms of distress occur, the patient should be advised to remain very quiet and refrain from sitting in an upright position.

Symptoms of Poisoning.—The usual symptoms of toxicity are deep stupor, fall in blood pressure, vasodilation, cyanosis, slow weak pulse, and slow respiration. If the drug was given by mouth, there may be vomiting. Death usually occurs from sudden heart failure or failure of respiration.

Chloralism or chronic poisoning also occurs in cases of habituation in which case some tolerance to the drugs is developed. This condition seems to be comparatively rare. It results in degenerative changes of the liver and kidney, nervous disturbances, weakness, skin disorders, and gastrointestinal upsets

Other Chloral Hypnotics.—

Butylchlorate Hydrate, N. N. R., a crystalline white powder with bitter taste and pungent odor. The adult dose is 0.3-1 Gm. and may be given orally in capsules. Its action is much like that of chloral hydrate and appears to have some analgesic effect as well.

Chlorobutanol, U. S. P., a colorless crystalline substance miscible with water, alcohol, ether, and the volatile and fixed oils. It does not cause gastric irritation and because it has some anesthetic properties, it is used in wounds either in the form of dusting powders or in solution. The hypnotic oral dose is 0.3 to 1.3 Gm., given as tablets or capsules. Chloretone is a brand of chlorobutanol.

B. Paraldehyde.—Paraldehyde, a polymer of acetaldehyde, is a colorless transparent liquid with a strong pungent odor and a burning disagreeable taste. It is only slightly soluble in water but freely so in oils and in alcohol.

Pharmacologic Action.—Paraldehyde depresses the central nervous system much the same as chloral hydrate. It is a rapidly-acting hypnotic, sleep resulting in 15 to 20 minutes after a hypnotic dose. The sleep closely resembles natural sleep.

Therapeutic doses do not depress heart action or respiration.

5. As an anticonvulsant in the treatment of epilepsy and in other convulsive states. (Not considered as efficient as Dilantin and Phenobarbital for this effect.)

6. To relieve headaches caused by mental excitement. Best results are obtained, however, if given with an analgesic.

F. Administration.—Bromides are always given by mouth in the form of capsules, tablets, or in specially flavored vehicles to disguise the disagreeable salty taste. Effervescent preparations are quite easy to take. They should be given after meals and with plenty of fluid to minimize the gastric irritation and the dehydrating effect of the medication. Administration is usually three to five times a day.

G. Some of the Bromide Preparations and Their Dosage.—

Potassium Bromide (Potassii Bromidum), U. S. P. Dosage: 1 Gm. (15 grains).

Sodium Bromide (Sodii Bromidum), U. S. P. Dosage: 1 Gm. (15 grains).

Elixir of Sodium Bromide (Elixir Sodii Bromidi), N. F. Dosage: 4 cc. (1 fluidram). Sodium Bromide 17.5 per cent in syrup, water and aromatic elixir, absolute alcohol about 6 per cent.

Tablets of Sodium Bromide (Tabellae Sodii Bromidi), N. F. Dosage: 1 Gm. (15 grains).

Elixir of Three Bromides (Elixir Bromidorum Trium), N. F. Dosage: 4 cc. (1 fluidram).

A mixture of sodium, potassium, and ammonium bromide.

Elixir of Five Bromides (Elixir Bromidorum Quinque), N. F. Dosage: 4 cc. (1 fluidram). A mixture of sodium, potassium, ammonium, calcium, and lithium bromides.

Carbromal, N. F. Dosage: 0.5 Gm. (7½ gr.), given in cold water. Acts as a sedative and mild hypnotic.

Bromural, N. N. R. Useful as a sedative and hypnotic in functional nervous disease. Dosage: 0.3 Gm. as a sedative, 0.6 Gm. for hypnotic effect.

H. Toxic Symptoms.—*Acute bromide poisoning* is comparatively rare. Large doses, however, may produce deep stupor, ataxia, extreme muscular weakness, and collapse. Treatment consists of stopping the drug and giving large quantities of physiologic salt solution to hasten the excretion of the drug.

Chronic poisoning.—Repeated administration of bromides often leads to a condition known as *bromism*. This condition varies according to individual susceptibility. The first symptom may be a

be allayed. After the bromides have been given long enough to build up the level in the blood the mind becomes less alert, special senses are less keen, the patient becomes apathetic, relaxed, indifferent and more or less drowsy. Nervous excitement, worry, and anxiety are relieved. Sleep, however, after large doses is not necessarily refreshing but may be followed by a drowsy hangover and a sense of weariness. Reflexes are diminished, an example of which is the disappearance of the gagging reflex when the fauces is irritated.

2. *Circulatory System*.—Ordinary doses of the bromides have little effect on circulation. They sometimes favorably influence cardiac disturbances due to an abnormal irritability of the central nervous system. Very large doses depress the heart and vasoconstrictor center.

3. *Alimentary Canal*.—Although bromides are given to allay vomiting of central origin, they have no effect on the alimentary canal, with the possible exception of producing nausea and vomiting when large doses are given. This is attributed to irritation by their saline action.

The bromides of potassium, ammonium, and sodium have identical actions, but the ammonium ion is somewhat stimulating and the potassium ion depressing, while the sodium ion is neutral in effect.

D. Absorption, Distribution, and Excretion.—Bromides are rapidly absorbed and are excreted almost entirely in the urine. There is a tendency to accumulation since they are not excreted as rapidly as absorbed.

Bromides when absorbed occur in all the secretions and fluids of the body. Traces are found in sweat, milk, in the hair, and other places where chlorides occur naturally. The brain and spinal cord do not contain any more than other organs, and never approach the concentration found in the blood plasma.

E. Main Therapeutic Uses.—Bromides are given primarily as anti-convulsants and as sedatives. They are not, however, preparations of choice if a rapid action is desired. Sedation is not obtained by a single dose but rather by consecutive doses in order to obtain the desired level of the bromide in the blood.

Some of the uses are as follows:

1. To relieve nervous tension in hysterical states, nervous gastrointestinal conditions, and in exophthalmic goiter.
2. To check vomiting of pregnancy, seasickness, etc.
3. To quiet patients with certain cardiac disorders and decrease cardiac excitability.
4. To decrease sexual hyperesthesia associated with some mental conditions, adult circumcision, etc. (Anaphrodisiacs.)

port should reach the physician in charge before the anesthetic is started. When morphine is given an hour or an hour and a half before surgery, the peak of the respiratory depression is likely to have passed. Atropine or scopolamine may be given alone or with morphine to check secretions of the mouth and respiratory tract, particularly if the anesthetic to be given is irritating to mucous membranes.

The diet on the day or two prior to general anesthesia should preferably be light, comparatively high in carbohydrate and protein, and low in fat. Several hours should elapse since the last meal and an enema is usually given to cleanse the lower bowel and thus help to prevent accidental defecation at the time of operation, and distention after the operation. Laboratory tests and procedures which are a part of a routine physical examination will focus attention on the cardiac, renal, hepatic, and pulmonary functions of the patient. The results of these tests will not only often determine the choice of the anesthetic but may also determine the probability of successful anesthesia.

STAGES OF ANESTHESIA

Anesthesia is produced by a progressive depression of the central nervous system. As the anesthetic increases in the blood, there is a corresponding increase in the nervous system. The first portion to be depressed is the cerebrum, then the cerebellum and spinal cord, and finally the medulla. Sensory reactions are lost before motor ones. All sensation is not lost simultaneously, a point to be remembered both when the patient is receiving the anesthetic and when he is recovering from it. Patients often hear things not intended for their ears because they were believed to be entirely unconscious when they were only unable to speak or direct their movements. The stages of anesthesia vary somewhat with the choice of anesthetic, speed of induction, and skill of the anesthetist. ✓

I. Stage of Analgesia or Stage of Local Irritation and Diminished Sensation.

This stage begins with the first inhalation and lasts until consciousness is lost. The difficulty of getting air through the mask, and the irritating effect of some of the anesthetic agents on the mucous membranes cause choking, coughing, flow of tears and saliva, and rapid irregular breathing. These reactions can be avoided to some extent by gradual induction and by the skill of the anesthetist in gaining the cooperation of the patient. The senses become less acute, the body feels stiff and unmanageable, the face

bromide acne which is seen on the face, chest, and back. The cause of the skin disturbance is not definitely known but is probably due to a peculiar sensitization of the skin by the bromide ion. Other poisonous symptoms from long-continued use are, salty taste in the mouth, foul breath, gastrointestinal disturbance, mental depression, faulty memory, pronounced apathy, ataxia, slurred speech, muscular weakness, malnutrition, and anemia. As a rule the symptoms of bromism rapidly abate if the drug is withdrawn.

I. Contraindications.—Bromides should be given with caution to patients with advanced arteriosclerosis, debilitation, and dehydration. A state of delirium can be rather easily produced in the patient with cerebral arteriosclerosis. Poor renal function, chronic alcoholism, malnutrition, mental depression are all conditions in which bromide therapy is not indicated. Since bromides are not good analgesics, their use when the patient is in pain may cause delirium. Bromides are also counterindicated for patients who are to receive the drug for long periods of time unless they can be kept under close medical observation.

III. ANESTHETICS

Anesthetics are drugs given to produce loss of sensation. General anesthetics produce this condition throughout the entire body by cutting off all sensory impulses to the brain, thus causing unconsciousness and sleep. Local anesthetics abolish sensations only in the region of application.

General Anesthetics

Surgical anesthesia refers to a depth of anesthesia necessary for surgical operations. Basal anesthesia is a lighter degree of anesthesia obtainable from a large dose of certain preanesthetic medications. Tribromethanol (avertin) is a good example of a basal anesthetic drug.

Satisfactory anesthesia is partly dependent upon the preparation of the patient. Several hours of restful sleep, and relief from worry and anxiety help to get the patient into a state conducive to good anesthesia. Sedative and hypnotic drugs are usually administered the night before, as well as the morning of, the operation. One of the barbiturates is frequently chosen as a preanesthetic medication although morphine is also used. A disadvantage encountered in the use of morphine is related to its depressant action on the respiratory center. Any marked slowing of respiration should be noted by the nurse before taking the patient to surgery and a re-

REQUIREMENTS OF AN IDEAL ANESTHETIC

1. It is highly desirable that the anesthetic agent have a wide safety range; considerable difference should exist between the therapeutic and the toxic dose.
2. It should produce anesthesia rapidly and not be unpleasant to take.
3. The recovery should be rapid and free from discomfort.
4. The anesthetic should be readily excreted from the body without damage to body tissues.
5. It should produce maximum muscular relaxation and should not increase capillary bleeding.
6. It should be of such potency that the levels of anesthesia are easily controlled and that oxygen may be freely administered with it.
7. It should be a stable substance and not explosive.

There is no known anesthetic which fulfills all of the above requirements, but they may be used as a measuring stick in evaluating the properties of the various anesthetic agents.

The use of anesthesia in surgical operations began in this country in 1846 when the action of ether was first demonstrated to the public by Jackson and Morton. The next year, Simpson of England used chloroform for the same purpose, and since that time ether and chloroform have been the two universally accepted anesthetics. Ethyl chloride, nitrous oxide, and ethylene are also used for short operations. Ether is one of the oldest and best known of the anesthetic agents. It is given by inhalation.

Ether

Physical and Chemical Properties.—Ether, U. S. P., is a clear colorless fluid prepared by the action of sulfuric acid on alcohol. It contains 96 to 98 per cent of ethyl oxide with alcohol and water. It is very volatile and has a suffocating odor and burning bitter taste. Ether vapor is very inflammable and should be kept away from gas flames or fire. Mixtures of ether and oxygen are explosive. It is decomposed by light and air and therefore should be kept in well-stoppered bottles.

Ether is a good solvent for fats, oils, resins, and adhesive plaster.

Pharmacologic Action and Results of Action.—

Local Action.—When applied to the skin and allowed to evaporate, ether rapidly cools the skin. If it is not allowed to evaporate, it acts as a rubefacient. Ether irritates mucous membranes and causes increased secretion of mucus and increased secretion of saliva in the

is flushed, pupils are dilated but react to light, and the pulse is rapid. Numbness and loss of sensation gradually spread over the body:

II. Stage of Excitement.—This stage varies greatly in different individuals. It is not always seen in adults and is frequently absent in children. In some people there is merely tremor, or stretching of the limbs, or irregularities in respiration; but in others, especially habitual users of alcohol, there is great excitement and violent movements. This stage begins with movements of the arms designed to push the mask away or to enable the patient to rise. Then the other muscles are involved in the movement and the patient may struggle, sing, shout, laugh, swear, or talk. These symptoms of excitement are related to dreams connected more or less with the operation, but determined by the natural mode of thought of the individual. When the anesthetic is taken quietly in the privacy of the home, less excitement is seen. In this stage the pulse is rapid, the face is flushed or cyanotic, respiration is irregular and the pupil is dilated.

Exaggerated respiratory reflexes are responsible for irregular respiration and may result in an uneven absorption of the anesthetic agent into the blood, thus constituting one of the greatest dangers in anesthesia. Correct use of the preanesthetic medication is important to avoid accident in this stage. Spinal reflexes are still present, hence *muscular relaxation is insufficient for any but superficial surgery.*

III. Stage of Surgical Anesthesia.—In this stage the respiratory irregularities disappear and respiration becomes full and regular, although somewhat slower and sometimes stertorous. The pulse remains full and strong but is slower than in the previous stages. The face is calm and expressionless and may be flushed, or even cyanotic. The muscles become increasingly relaxed for reflexes are gradually abolished as anesthesia becomes deeper. Most abdominal operations cannot be done until the peritoneal reflexes are abolished and the abdominal wall is soft. With an anesthetic like ether the third stage may be kept up for hours with little change by the repeated administration of small amounts of the drug. There is a progressive loss of body temperature as the anesthetic state continues. The pupils are contracted and react sluggishly to light. During the recovery period, the patient retraces the stages of anesthesia in reverse order.

IV. Stage of Medullary Paralysis (Toxic Stage).—This stage is characterized by respiratory arrest and vasomotor collapse.

because its analgesic effect cannot be obtained fast enough unless the pains are coming regularly and each pain is carefully anticipated. Ether is sometimes mixed with oil and given rectally to diminish pain of early labor.

Ether produces diminished peristalsis and tone in the smooth muscle of the gastrointestinal tract and may be the cause of atony of these organs following abdominal operations.

Excretion.—Ether is rapidly excreted by the lungs, although traces of it may be retained for several hours. Carbon dioxide inhalations facilitate the excretion.

Uses.—

1. The greatest value of ether lies in its use as a general anesthetic, particularly for long operations, and when deep muscular relaxation is necessary. It has a wide safety range.

A combination of nitrous oxide gas and ether is now commonly used, and various types of apparatus have been devised to measure and control the amount of vapor inhaled and to provide the necessary amount of oxygen and moisture and warmth. By this method the unpleasant suffocating effects of ether and much of the excitement are avoided.

2. To check convulsive seizures associated with tetanus and strychnine poisoning.

3. As a carminative, to lessen the formation of gas in the stomach and intestine.

4. As a solvent to cleanse the skin prior to surgical operation.

Preparations and Dosage.—

Ether (Aether), U. S. P. The dose of ether varies with the patient and the degree of anesthesia desired.

Ethyl Oxide (Aethylis Oxidum), U. S. P. Solvent ether—not to be used for anesthesia.

Compound Spirit of Ether (Spiritus Aetheris Compositus, Hoffmann's Anodyne), N. F. Dosage: 4 cc. (1 fluidram). Used chiefly as a carminative given orally.

Symptoms of Poisoning (Ether Anesthesia).—

1. Relaxation of sphincter muscles.
2. Widely dilated pupils which fail to react to light.
3. Slow shallow, irregular, gasping respiration.
4. Pulse begins to get weak and irregular.
5. Blood pressure drops rapidly.
6. Skin becomes gray, cold, and clammy.

mouth. When moderately diluted, it acts as a carminative in the digestive tract. Nausea and vomiting may result from gastric irritation, although this effect may also result from a central stimulation of the vomiting center.

Systemic Action.—The systemic action of ether has been characteristically described in the description of the stages of anesthesia. After absorption of sufficient quantities of ether, there is a progressive depression of the central nervous system, beginning with the higher intellectual centers and progressing to the sensory and motor centers, i.e., cerebral cortex, basal nuclei, cerebellum, spinal cord, and finally the medullary centers. Learned reactions are lost first and sensory functions before motor functions. Consciousness is gradually lost and gradually complete relaxation of muscles and immobility occur. The reflexes of the spinal cord are first stimulated, then depressed, and finally abolished.

Ether makes the heart beat faster and stronger during the induction period of anesthesia, although it becomes slower and somewhat weaker as anesthesia deepens. Ether produces peripheral vasodilation by slight central vasomotor depression and also by direct action upon smooth muscle of the blood vessels, particularly the peripheral vessels in the skin. The skin feels warm and the face is frequently red. Loss of considerable heat from the body is thus explained. The body temperature may be reduced several degrees during a long operation, hence the need of a warm operating room and a warm bed after the operation.

The respiratory center is reflexly stimulated by local irritation during the first stages of anesthesia which may result in uneven inspiration and sudden change in the amount of ether in the blood. Respirations are usually full and even during surgical anesthesia, although they become slower as the anesthesia lengthens.

The pupil during ether anesthesia is usually somewhat dilated in the first and second stages and contracted in the third stage. As the patient regains consciousness slight dilatation recurs. Sudden wide dilatation is a sign of possible danger, as it may mean the beginning of asphyxia.

There is evidence that ether is irritating to the kidneys as indicated by the appearance of albumin in the urine as well as scanty urine formation several hours postoperatively. Postoperative retention of urine may occur due to poor tone in the urinary bladder.

Contractions of the uterus are not much affected by moderate degrees of anesthesia but are slowed and lessened by deep narcosis. Ether is not an entirely satisfactory agent to relieve labor pain

Other Uses of Chloroform.—Spirit of Chloroform, N. F., like spirit of ether, is given by inhalation to check convulsions. It is also given internally to check the formation of gas in gastric fermentation and to relieve colic. In larger doses it is sometimes used as a vermifuge, but other vermifuges are safer and more efficient.

Chloroform liniment, U. S. P., is applied locally as a counterirritant to relieve pain. It is penetrating and powerful and may blister if its evaporation is prevented.

Methods of Administering Anesthesia.—The simplest method of giving ether or chloroform is by inhalation through a mask covered with gauze, which is placed over the patient's nose and mouth. The anesthetic is poured on the mask drop by drop and becomes thoroughly mixed with the air before being inhaled by the patient. The respiration and pulse and blood pressure are watched very closely to detect the first signs of danger.

Choice of Anesthetics.—Ether is much less liable to produce dangerous results than chloroform and should be used unless some special condition contraindicates it. It may be advisable to give chloroform in conditions in which the respiratory tract is irritated or inflamed, or where excitement must be avoided as much as possible. Chloroform is more pleasant to take, produces deeper anesthesia with smaller quantities of drug and can be used safely in the presence of an open flame. It has a wider use in tropical countries than in the United States. It is used here largely as an emergency anesthetic in convulsive poisoning or in surgical or obstetric cases in a home where there are open flames.

Dangers of Chloroform Anesthesia.—The chief danger is that of cardiac syncope or sudden heart failure which causes most of the deaths occurring under chloroform.

The symptoms are as follows:

Sudden irregularity or disappearance of pulse.

Deathlike pallor of the face.

Dilatation of the pupils.

Failure of the reflexes.

Sudden change to deep, labored, and gasping breathing.

Rapid failure of respiration.

The sudden heart failure often occurs in the first stage of anesthesia, when only a few drops of chloroform have been administered, and indicates abnormal irritability of the heart muscle for chloroform.

The treatment for sudden heart failure consists in lowering the head and elevating the limbs of the patient, giving artificial respiration and massaging the area over the heart. Occasionally the patient recovers, but more often the results are fatal.

Other dangers of ether include those which occur when vomitus or mucus is aspirated and asphyxia threatens or when relaxed tongue muscles permit it to slip back in the throat and obstruct the breathing. The jaw must be supported during anesthesia, the tongue drawn forward, and mouth and throat cleansed of mucus as may be necessary.

Treatment of Poisoning.—

1. Stop the anesthetic.
2. Give artificial respiration.
3. Administer oxygen and carbon dioxide.
4. Give heart and respiratory stimulants such as caffeine, coramine, atropine, etc.
5. Elevate the foot of the bed or operating table.

Contraindications.—

1. Because of its irritant action on the mucous membranes of the respiratory tract, ether is contraindicated in pulmonary tuberculosis, bronchiectasis, and in acute pulmonary infections.
2. In patients with advanced renal disease.
3. When an open flame or cautery must be used, unless special precautions are taken.

Chloroform

Chloroform, U. S. P., is a heavy, clear, colorless, volatile fluid prepared by the action of chlorine on alcohol. It has a characteristic odor and hot, sweetish taste. Chloroform should be protected from the light by storing in a dark place or in dark, well-stoppered bottles. It deteriorates readily under the influence of heat, light, and air, and is then unfit for general anesthesia. For this reason, the vapor should not be allowed to come in contact with a flame.

Action and Uses.—Chloroform is administered chiefly by inhalation for the production of general anesthesia.

The symptoms produced by chloroform may be divided into three stages as in the case of ether, and the general effects of chloroform are similar to those of ether, but there are certain important differences between the two anesthetics.

The stage of surgical anesthesia is more dangerous than with ether. Chloroform is much more depressing to the heart, paralyzing the cardiac muscle so that there is a gradual but progressive fall of blood pressure. The depressant effect on the respiration is also much greater. Chloroform is more pleasant to take, produces anesthesia more quickly and with less excitement, and is not as irritating to the respiratory tract.

Other Uses of Chloroform.—Spirit of Chloroform, N. F., like spirit of ether, is given by inhalation to check convulsions. It is also given internally to check the formation of gas in gastric fermentation and to relieve colic. In larger doses it is sometimes used as a vermifuge, but other vermifuges are safer and more efficient.

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Delayed Dangers of Anesthesia.—The dangers of anesthesia are not all over when the patient has been returned to bed and has regained consciousness. Fatty changes in the heart, liver, and kidneys and albuminuria may follow several days after the administration of chloroform, and bronchitis, pulmonary edema or pneumonia, after ether.

Vinyl Ether (Vinethene)

Vinethene, U. S. P., is a clear colorless fluid which greatly resembles ether. It is more volatile but about as inflammable and explosive as ordinary ether. It acts more rapidly than ether which means that the toxic stage is easily reached. The patient must be watched with unusual care to prevent overdosage. Surgical anesthesia occurs two or three times as quickly as with ordinary ether.*

Respirations are quiet and slightly slower than with ether; blood pressure has a tendency to fall slightly, and muscular relaxation is about the same as with ether.

Prompt recovery follows cessation of the administration of the anesthetic, the patient being completely conscious and able to move about within a few minutes. Vinethene is useful in dentistry, during labor and postpartum repair procedures, and also as an induction anesthetic prior to another anesthetic agent.

The signs of anesthesia are somewhat different from those seen in ether anesthesia. Of major importance is the fact that the eye signs, usually depended on in anesthesia, are entirely unreliable. The most important single signs to follow in determining the extent of anesthesia are the rate, depth, regularity, and smoothness of respiration. Although there is occasionally an increased secretion of mucus during maintenance, even when atropine is administered, postoperative complications have not been frequently encountered. Nausea and vomiting occur in about 5 per cent of the cases. As with most other anesthetic agents, age, cardiovascular disease, renal insufficiency or hepatic damage, particularly the latter, must be given due consideration as contraindications.†

Ethyl Chloride

Ethyl Chloride, U. S. P., is a colorless and very volatile liquid having an agreeable odor and a sweetish, burning taste. It is sold in hermetically sealed glass tubes and should be kept in a cool, dark place away from any possible contact with fire.

*Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*. The Macmillan Co., p. 73.

†New and Nonofficial Remedies, 1944, p. 107.

Ethyl chloride is used for minor operations in the form of spray to produce local anesthesia by refrigeration. When inhaled, it produces prompt anesthesia, which, however, is suitable only for very short operations, such as tonsillectomy in children. It is useful for inducing anesthesia before the administration of ether; but however brief its general effects, it is not without danger similar to that from chloroform.

Nitrogen Monoxide, U. S. P., Laughing Gas

Nitrogen monoxide or nitrous oxide, N_2O , is a colorless gas possessing a slight characteristic odor and a somewhat sweet taste. It is made by the distillation of ammonium nitrate. When nitrous oxide mixed with air is inhaled, it produces a condition similar to a certain stage of alcoholic intoxication. The patient feels merry and good-natured, laughs, and talks, but does not go to sleep.

When the pure gas is inhaled, after a few deep inspirations, the face becomes deathly pale and the patient sinks into unconsciousness. If administration is continued, cyanosis follows and death may result from asphyxia. If the inhalation of gas is stopped before marked cyanosis comes on, there is rapid return to consciousness with no aftereffects. A safe anesthesia of from only 30 to 60 seconds is possible by this method, which is used mostly in dentistry, in brief operations and in obstetrics.

More prolonged anesthesia with nitrous oxide can be safely produced by giving the necessary amount of oxygen along with the gas. Appliances are in use for giving these together and increasing or reducing the proportion of either one as the patient's condition requires. Relaxation of the muscles is not as complete as it is under ether or chloroform, but the method is frequently employed as a preliminary to the induction of anesthesia with ether or chloroform.

Nitrogen monoxide is supplied by the pharmacist, in the compressed state as a liquid in steel cylinders. When the pressure is decreased, the liquid returns to the gaseous state, and is inhaled by the patient from an inhalation apparatus.

Ethylene, U. S. P.

Ethylene is a highly volatile colorless gas with a slightly sweet taste and not unpleasant odor. Ethylene is explosive and inflammable when mixed with a certain amount of oxygen. Explosiveness is its greatest disadvantage.

In the early days of its use, there were some explosions, but this danger is now easily avoided. The explosive concentration (3.2

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†New and Nonofficial Remedies, 1944, p. 107.

with ether. Relaxation of striated muscle is marked, but the abdominal muscles sometimes regain their tone too quickly. The uterine and intestinal muscles are not relaxed. Recovery is rapid, but postanesthesia nausea is more frequent than with nitrous oxide. It is administered by inhalation, preferably by the carbon dioxide absorption technic. Danger is signaled by circulatory changes, such as slowing of the heart and arrhythmias. Changes in the pulse, slowing to fifty beats or a sudden quickening, should warn the anesthetist to decrease the anesthetic.

Uses.—Cyclopropane has been successfully used as a general anesthetic for all kinds of operations. It is particularly useful when it is of marked importance to supply plenty of oxygen to the tissues, as in patients with circulatory complications, pregnancy, exophthalmic goiter, anemia, and pulmonary complications. It has been approved as an anesthetic in chest surgery because of the quiet respirations and lack of spasm of smooth muscles along the respiratory tract. It has been especially recommended in obstetrics because its action is so rapid that one or two whiffs may be used for each pain and it does not interfere with contractions of the uterus or with the respiratory system of the newborn. Its administration requires careful watching, however, and until it is further developed, it should be used as a general anesthetic only, under the direction of an experienced anesthetist.

Basal Anesthetics

By basal anesthesia is meant the induction of unconsciousness by a nonvolatile anesthetic or soporific before the production of general anesthesia. It is advocated to allay emotional stress, to reduce the amount of the general anesthetic, and to make the induction of general anesthesia smoother and more easily controlled.

Tribromoethanol, U. S. P. (Tribromoethyl Alcohol; Avertin)

Tribromoethanol is chemically related to ethyl alcohol and to chloral. It is a white crystalline powder with a slight aromatic taste and odor. It is unstable in light and air and sparingly soluble in water but very soluble in amylene hydrate. It is therefore marketed as Avertin with Amylene Hydrate. The drug was introduced as a general anesthetic, but in the full doses required for anesthesia, it is strongly depressant to the respiratory center. Furthermore, avertin is a nonvolatile drug and it is difficult to control the depth of narcosis once the drug is administered. It is used mainly as a basal anesthetic. Solution of Tribromoethanol is administered rec-

per cent), it has been found, diffuses no further than two feet from the mask, and it is stated to be no more explosive than ether-oxygen or ether-nitrous oxide-oxygen under comparable precautions. No electrical devices should be employed within three or four feet of the mask. Caution against open flames, the use of cautery, and sparks should be observed while it is used.

Ethylene was recommended as an anesthetic by Luckhardt and Carter in 1923. Since then its use has become quite general. It has a direct depressant action on the nervous system with loss of motor reflexes when a concentration of 90 per cent ethylene and 10 per cent oxygen or less is used. Analgesia comes on readily and long before surgical anesthesia is established. It is a more powerful anesthetic than nitrous oxide, less powerful than ether, but in most instances it is efficient. Unlike ether, it causes no respiratory irritation and does not cause increased salivary secretion.

In spite of its explosiveness and the fact that muscular relaxation is less easily achieved than with ether, ethylene is almost an ideal anesthetic. Its rapidity of action, safety range, and rapid recovery without aftereffects are very satisfactory. The induction is rapid and pleasant; relaxation is not accompanied by cyanosis or sweating and respiratory, vasomotor, or metabolic disturbances are not encountered.

Dosage.—Ethylene for anesthesia is available compressed in metal cylinders. It is used mixed with 10 per cent oxygen. Care must be used to supply enough oxygen to prevent asphyxiation. The technic must be learned from a trained anesthetist. Morphine may be used as a preliminary agent. It facilitates the administration of ethylene and permits the use of lower concentrations, but it is not essential.

Cyclopropane, U. S. P.

Cyclopropane is a colorless gas, heavier than air, inflammable and explosive when mixed with air or oxygen. It has a mildly pungent not unpleasant odor. It is quite stable and is stored in metal cylinders as a liquid under pressure.

Cyclopropane gives evidence of being a valuable anesthetic. It has a wide margin of safety and is a very potent anesthetic gas so that adequate oxygen can always be given with it—to the extent of 20 per cent or more. It produces anesthesia in concentrations as low as 4 per cent. It causes no irritation and no change in respiration until very distinct depression is produced. The muscular relaxation is greater than with nitrous oxide, but not as complete as

by using pentothal sodium intravenously along with a mixture of 50 per cent nitrous oxide and 50 per cent oxygen.

The intravenous anesthesia relieves the pain associated with the injection of the main anesthetic or produces the desirable numbness when the local, regional, or spinal anesthetic is wearing off. Intravenous anesthesia is also used to induce ether or gas anesthesia quickly or as a preliminary to open drop ether anesthesia for refractory patients.

Intravenous anesthesia provides a smooth, easy, pleasant induction for the patient, relatively uneventful recovery, rare complications and offers no fire or explosion hazard. On the other hand, control is maintained less easily than with an inhalation anesthetic; there is some danger of thrombophlebitis, and sometimes difficulties are encountered in entering a vein in obese individuals or in children.

Intravenous anesthesia with barbiturates has been successfully used for treatment of simple fractures, cleansing of burns and skin lacerations, transportation of casualties, short oral operations, removal of sutures and painful dressings, and similar conditions.

Preparations.—

Pentothal Sodium, N. N. R. This barbiturate is chemically related to pentobarbital sodium. It is a sulfur-containing member of the barbiturate series.

Evipal Sodium, N. N. R. Evipal is very similar to pentothal sodium but less potent and very short acting.

TABLE II

ANESTHETIC FATALITIES FOLLOWING VARIOUS AGENTS RECORDED BY
DIFFERENT COLLECTORS (ISABEL SCHMITZ-DUMONT)*

ANESTHETIC AGENT	COLLECTOR	CASES	DEATHS	DEATH RATE
Ether	Gwathmey	294,653	65	1 in 4,533
Nitrous oxide ether	Gwathmey	64,242	10	1 in 6,424
Local anesthesia	Gwathmey	30,846	0	
Chloroform	Gwathmey	22,513	14	1 in 1,608
Ethyl chloride	Gwathmey	12,261	0	
Nitrous oxide oxygen	Gwathmey	11,081	0	
Ether	Miller	865,162	108	1 in 8,010
Nitrous oxide oxygen	Miller	80,483	2	1 in 40,241
Spinal anesthesia	Miller	34,747	56	1 in 620
Ethyl chloride	Miller	83,750	8	1 in 10,470
Nitrous oxide	Muller	602,960	50	1 in 12,260
Nitrous oxide	McKesson	500,000	41	1 in 12,500

*The Diplomat 11: 307 (Dec) 1939, published by The National Board of Medical Examiners.

The exactness of these figures may be questioned, but they show clearly that chloroform is the most dangerous.

tally in 2.5 per cent solution in warm distilled water at a temperature not to exceed 40° C. The ordinary maximum dose for basal anesthesia is 80 mg. of tribromoethanol (40 mg. of amylene hydrate) per kilogram of body weight. The total amount, however, should not exceed 6 to 8 cc. for women and 9 to 10 cc. for men, regardless of weight.*

In the amounts stated the drug produces drowsiness, amnesia, and sleep. It materially decreases the amount of inhalation anesthetic required in addition to providing a pleasant induction and a state of sedation which lasts well into the postanesthetic period. Careful nursing must attend the patient throughout the anesthesia and postanesthetic sleep to insure the maintenance of an open airway.

Avertin is of particular value as a basal narcotic for patients who are extremely nervous and apprehensive, because the drug can be given as a retention enema to the patient while he is in his own room. He will go to sleep and avoid the mental distress and respiratory irritation associated with the induction of a number of general anesthetics. Avertin is also given to control convulsive seizures, maniacal attacks, and to break the vicious cycle of status asthmaticus.

Avertin is contraindicated for patients with impaired liver and kidney function, chronic alcoholism, diseases of the rectum and colon, heart failure, acidosis, toxemia, and severe hypothyroidism.

INTRAVENOUS BARBITURATES

Evipal Sodium, N. N. R., and Pentothal Sodium, N. N. R., are the barbiturates which have proved to be most satisfactory as intravenous anesthetics. Although the action of these drugs is similar, most authorities believe that pentothal sodium because of its greater potency is the better anesthetic of the two.

When used for anesthesia the usual stages of anesthesia may not be apparent because consciousness is lost very rapidly. The patient is likely to go to sleep in the middle of a sentence. The use of 2.5 per cent solutions given in intermittent injections has replaced the original method of giving stronger solutions. Large doses have been found likely to cause dangerous respiratory depression and a delayed thrombophlebitis.

Intravenous anesthesia is believed suitable for many short or minor operations or where muscular relaxation is not necessary. It is also employed as a part of balanced anesthesia in which a pre-anesthetic narcotic like nembutal or morphine and atropine is given. Then a local regional or spinal anesthetic is introduced (or ended)

*N. N. R., 1944, p. 109

Action.—The most important use of cocaine is based on its ability to block nerve conduction when applied locally. It has no effect on unbroken skin, but when applied to an abraded surface, mucous membrane, or when injected under the skin, it produces insensibility to pain by paralyzing pain receptors and nerve endings. Sensation is completely recovered when the drug is eliminated.

After absorption, cocaine stimulates the central nervous system from above downward. When a moderate degree of absorption takes place, the result is a state of mild stimulation. The pulse is stronger and more rapid, blood pressure is elevated, the respirations are faster and deeper, and all the activities of the brain are increased. The patient is more active and talkative, more alert mentally, and feels exhilarated and happy. With increasing absorption, depression rather quickly follows stimulation. The higher centers are depressed first; death is due to respiratory paralysis. Cocaine dilates the pupil of the eye as well as produces anesthesia of the cornea and vasoconstriction of the conjunctiva and sclera. Accommodation is only slightly affected.

Administration.—Epinephrine is usually given with cocaine to produce vasoconstriction and also to localize and intensify the anesthesia. Cocaine and its derivatives may be given by the following methods although cocaine itself is usually administered by the first method and the derivatives are given by injection due to the fact that they are less toxic than cocaine.

a. *Surface Anesthesia.*—This is accomplished by swabbing or painting the mucous membrane with a 10-20 per cent solution (cocaine). It is used as a method of anesthetizing the nose, throat, and pharynx, and prior to painful instrumentation.

When cocaine is applied to the conjunctiva, it is used in 1 to 4 per cent solutions. For injections into the urethra, very dilute solutions, from 1 in 1000 to $\frac{1}{2}$ per cent are employed, because of the dangers of absorption. Their efficacy may be increased by the addition of 0.5 per cent of sodium bicarbonate to the solution immediately before using it.

b. *Infiltration Anesthesia.*—The anesthetic agent is injected into the tissue in weak solution. If the area is very small, a more concentrated solution may be used than if the number of injections must be great.

c. *Regional Anesthesia* is accomplished by injection of the local anesthetics first into the skin of the area, and then into the neighborhood of the sensory nerves which supply the area.

d. *Block Anesthesia* is accomplished by injecting the anesthetic directly into the nerve which supplies the part in which the anesthesia is desired.

TABLE III

INCIDENCE OF PULMONARY COMPLICATIONS FOLLOWING VARIOUS ANESTHETIC AGENTS RECORDED BY DIFFERENT COLLECTORS
(ISABEL SCHMITZ-DUMONT)

ANESTHETIC AGENT	COLLECTOR	COMPLICATIONS
Ether	Size	3.1%
Gas oxygen	Size	1.8%
Local	Size	7.5%
Ethylene ether	Lundy	8.8%
Spinal	Campbell	0.7%
Cyclopropane	Burford	0.9%

HELIUM IN ANESTHESIA

Helium is a colorless, odorless gas, and, next to hydrogen, is the lightest element. Helium is one of the rare gases and constitutes less than 1 per cent of the atmosphere.

Barach, 1934, reported the use of helium as a new therapeutic gas. It is intirely inert, but in anesthesia it is used as a diluent, and makes breathing seem easier to the patient.

Local Anesthetics

Although local anesthetics do not rightfully belong under central depressants, for convenience of study they are presented after the general anesthetics.

Local anesthetics are drugs which in sufficient concentration are capable of blocking nerve conduction along both sensory and motor fibers. When carefully controlled concentration is used, it is possible to produce loss of sensation without motor paralysis because sensory fibers are always affected before motor fibers. Most local anesthetics, when used properly, can produce anesthesia in a certain definite portion of the body without producing a systemic effect. Some of the anesthetic agents (cocaine) exert not only a local action but also a central one. The synthetic agents, however, have slight effect on the central nervous system and hence do not cause addiction.

Cocaine, U. S. P.

Source.—Cocaine is one of the oldest anesthetics and still one of the most important. It is the alkaloid derived from the leaves of the coca shrub which grows in Peru and other parts of South America. The natives of those countries chew the leaf to give them added energy and ability to endure hunger and fatigue. In medicine, cocaine is used chiefly in the form of cocaine hydrochloride which occurs as a white crystalline powder which is freely soluble in water or alcohol.

Action.—The most important use of cocaine is based on its ability to block nerve conduction when applied locally. It has no effect on unbroken skin, but when applied to an abraded surface, mucous membrane, or when injected under the skin, it produces insensibility to pain by paralyzing pain receptors and nerve endings. Sensation is completely recovered when the drug is eliminated.

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d. *Block Anesthesia* is accomplished by injecting the anesthetic directly into the nerve which supplies the part in which the anesthesia is desired.

e. *Spinal Anesthesia*.—To produce spinal anesthesia the agent is slowly injected into the spinal canal. Anesthesia over the body below the point of injection is produced in about twenty minutes. This is one of the most dangerous methods and necessitates a specially trained and experienced anesthetist.

Poisoning.—Acute toxic symptoms are likely to occur if the drug is absorbed rapidly, whereas slow absorption is relatively harmless, permitting destruction of the drug in the body. If excessive absorption takes place, either from overdoses given hypodermically or from too extensive local applications, these additional toxic symptoms occur: headache, excitement, dizziness, palpitation and fainting, sometimes convulsions and finally collapse. Death may occur in a few minutes from respiratory paralysis.

Treatment.—In mild or excited cases, treatment consists in keeping the patient quiet in bed and applying ice caps to the head. In severe cases, artificial respiration and the injection of epinephrine are indicated. If an overdose has been taken by mouth, the stomach should be washed out at once and the toxic symptoms treated as they appear.

Cocaine Habit.—This habit is acquired either from frequent medicinal use of cocaine or deliberately for the pleasurable excitement the drug produces. Addicts usually induce others to acquire the habit and assist each other in obtaining this and other habit-forming drugs. The tolerance for cocaine is considerable and the strength of habit is such that it is doubtful whether it is ever abandoned voluntarily. Continued use of the drug results in chronic poisoning. The earliest effects may be digestive disturbances, loss of appetite and weight, but the nervous system suffers most and gradual degeneration of mind and morals, as in opium habit, usually results. Sleeplessness, tremors, spasm, delirium and insanity are some of the consequences of long-continued use. To help combat the danger of habituation, the Harrison Narcotic Law makes the refilling of prescriptions for cocaine illegal.

Official Preparation.—

Cocaine Hydrochloride (Cocainae Hydrochloridum), U. S. P. Dose: 15 mg. ($\frac{1}{4}$ gr.).

COCAINE DERIVATIVES

There are many cocaine derivatives which are used more commonly than cocaine for local anesthesia, because they are less toxic. Procaine (novocain) is probably the most popular of this group.

Procaine, U. S. P. (Novocain)

Procaine is an artificial alkaloid used as a local anesthetic. It is not as valuable as cocaine for application to mucous membranes or to the conjunctiva, but is equally efficacious for injection anesthesia and is very much less dangerous. It does not constrict the blood vessels and does not dilate the pupil, has no central toxic action, and is not habit forming.

Administration.—For infiltration anesthesia, novocain is used in solutions of 0.25 Gm. (4 grains) in 100 or 50 cc. of physiologic sodium chloride solution to which 5 or 10 drops of epinephrin solution (1:1000) are added. For instillations and injections, solutions of 0.1 Gm. (1½ grains) in 10 or 15 cc. (150 or 225 minims) of sodium chloride solution are used; in operations on the nose and throat, 5 to 20 per cent solutions may be employed with the addition of 6 to 8 drops of epinephrine solution (1 to 1000) to each 12 cc. of solution. For conduction anesthesia, solutions of 0.5 to 2 per cent, preferably with the addition of 1 per cent of potassium chloride and 1 mg. of epinephrine hydrochloride for each gram of procaine are used. Procaine solution is also used for spinal anesthesia, potassium chloride 1 per cent being added. When injected into the spinal canal posterior to the cord, it produces insensibility to pain below the point of injection.

Poisoning.—Serious toxic symptoms are very rare. Mild symptoms are sometimes seen. These symptoms are weakness, mental confusion or excitement, pallor, weak pulse and slowed respiration. Such symptoms may result from faulty administration or individual sensitivity.

Official Preparation.—

Procaine Hydrochloride (*Procainae Hydrochloridum*), U. S. P. (Novocain). Dosage: 0.5-1 per cent solution. By subcutaneous injection up to 1 Gm. (15 grains).

Phenacaine Hydrochloride (*Holocaine*), U. S. P., is used chiefly in a 1 per cent solution as a local anesthetic in ophthalmology. It is as efficient in this field as cocaine and more rapid in action, but causes considerable smarting.

Tropococaine, Stovaine, Eucaine, and Pontocaine (1 per cent) are other synthetic drugs which have similar actions and use.

Butacaine Sulfate (*Butyn Sulfate*), U. S. P., is the sulfate of a base, resembling the base of procaine hydrochloride. It is used especially for surface anesthesia for the eye, nose, and throat. A one per cent solution is as effective as a one per cent solution of holocaine,

and more efficient than one per cent cocaine. It is more toxic than cocaine but less is needed to produce anesthesia. A 2 per cent solution is usually employed.

LOCAL ANESTHETIC WHICH ACTS BY FREEZING

Ethyl Chloride, U. S. P., is commonly used as a local anesthetic in minor operations. It is a colorless, and very volatile liquid, with a pleasing odor and sweetish, burning taste. It comes in hermetically sealed glass tubes which are so constructed that the contents may be applied directly to the site in a fine spray, which produces anesthesia by refrigeration. Ethyl chloride should be kept in a cool place, remote from light or fire.

ANODYNES

An anodyne is a drug which relieves pain at the site of application. Its effects are due to changes in the sensory nerve endings in the skin. The anodynes include several drugs described under another classification; namely, belladonna, methyl salicylate, camphor menthol, and phenol. The extract of belladonna and the belladonna plaster and ointment are used as local anodynes for the relief of rheumatic and neuralgic pains and soreness. Methyl salicylate is used locally either in the form of the pure oil or in liniment as a counterirritant and anodyne in rheumatic swellings and neuritis. Camphor is similarly used. Menthol is often employed for the relief of pain in neuralgia and headache. The solid menthol in the form of menthol pencils is rubbed over the painful area. The inhalation of menthol vapor gives prompt relief in acute rhinitis. Phenol acts as a local anesthetic and is so used in a 1 per cent solution or in ointment to relieve itching.

Ethyl Aminobenzoate, U. S. P. (Anesthesin), is a white crystalline powder which is applied to painful wounds and ulcers of the skin and accessible mucous membranes. It is valuable for use after extractions and other dental operations. It is applied as a dusting powder, either pure or diluted, or in the form of ointment or suppositories.

IV. INTOXICANTS

Ethyl Alcohol

Ethyl alcohol has been known in an impure form since earliest times, and it is the only alcohol used in medicine to any great extent. Alcohol was formerly thought to be a remedy for almost all diseases. It is a colorless liquid, lighter than water with which it mixes readily. In concentrations above 40 per cent it is

Pharmacologic Action and Results of Action.—

A. Local.—Ethyl alcohol dries and desiccates cellular protoplasm thus exerting an astringent action. It irritates denuded skin, mucous membranes, and subcutaneous tissue. Considerable pain results from subcutaneous injections and when made into or near a nerve, it is likely to result in nerve destruction and anesthesia. Alcohol is rapidly evaporated from the skin, thus reducing skin temperature. When rubbed on the body surface, it serves as a mild counterirritant, dries and hardens the epithelium, and thus helps to prevent bed sores. However, its use on skin which is already dry and irritated is usually contraindicated. Seventy per cent solutions of alcohol (by weight) seem to exert the best bacteriocidal effects. High concentrations have a marked dehydrating effect but do not necessarily kill bacteria.

B. Systemic.—According to modern scientific authorities alcohol is not considered a stimulant (popular ideas to the contrary). It exerts a progressive and continuous depression on the central nervous system (cerebrum, cerebellum, cord, and medulla). Its action is comparable to that of the general anesthetics. The excitement stage, however, is longer and when the anesthetic stage is reached, definite toxic symptoms are present. The margin between the anesthetic and fatal dose is a narrow one. What sometimes appears to be stimulation results from the depression of the higher faculties of man's brain and represents the loss of learned inhibitions acquired by civilization. The results of the action of alcohol vary with the individual, his tolerance, and the presence or absence of extraneous stimuli. Small or moderate quantities produce a feeling of well-being, talkativeness, greater vivacity, and increased confidence in one's mental and physical power. The personality becomes expansive, and there is a general loss of inhibitions. The finer powers of discrimination, concentration, insight, judgment, and memory are gradually dulled and lost. Large quantities of the drug may cause excitement, impulsive speech and behavior, laughter, hilarity, and in some cases pugnaciousness. Others may become melancholy or unduly sentimental. The individual usually becomes ataxic, mutters incoherently, has disturbance of the special senses, is often nauseated and may vomit, and eventually lapses into stupor or coma.

The respiratory center is not depressed except by large doses.

Circulation.—Alcohol depresses the tone of the vasomotor center and in this way dilates the peripheral vessels, especially those of the skin. This causes a feeling of warmth. Because of the capillary dilation, more heat is lost from the surface of the body and more must be brought from the interior. This accounts for the fact that a drunken person may freeze to death more quickly than a normal

and more efficient than one per cent cocaine. It is more toxic than cocaine but less is needed to produce anesthesia. A 2 per cent solution is usually employed.

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any marked diuretic action on the kidney but because of the increased fluid intake which ordinarily accompanies the drinking of alcoholic liquors. If the patient has preexisting renal disease, there may be further damage to the kidney. Large and concentrated doses of alcohol are thought to injure the renal epithelium. A very large percentage of the alcohol ingested is oxidized in the body, chiefly in the liver. Alcohol cannot be stored and it does not form glycogen.

Since alcohol, after absorption, is distributed in the tissues of the body in *approximately* the same ratio as their water content, a rough estimate of the quantity taken may be obtained from an analysis of the blood and urine. Muehlberger in *Toxicology* by McNally, 1937, gives his analysis as shown in Table IV.

Since 70 per cent of the weight of a man is water, and $\frac{1}{13}$ of his weight is blood, the approximate intake of alcohol may be computed.

Therapeutic Uses.—

1. Alcohol is used locally as an astringent and antiseptic in the prevention of bed sores, in cleansing the skin, and in form of wet dressings over wounds.

2. Alcohol is an excellent solvent for many medicines and is often a medium for medicinal mixtures (spirits, elixirs, fluidextracts).

3. As a preservative for specimens.

4. Alcohol is used in the treatment and relief of pain associated with severe and protracted neuralgia. An injection of 80 per cent alcohol produces destruction of the nerve fibers which may persist for one to three years, or until regeneration takes place.

5. As a vasodilator in certain peripheral vascular diseases and sometimes to decrease frequency of attacks in coronary disease.

6. Alcohol is occasionally used as an appetizer or food accessory for patients with poor appetite, during periods of convalescence and debility.

7. Alcohol has been advocated for the treatment of a cold but only in so far as it makes the patient sleepy and drowsy enough to go to bed and stay there for a long sleep, is it of any marked value. Because of its action on the circulation, the constriction of superficial vessels is lessened and internal congestion relieved.

8. Alcohol is used as a hypnotic and antipyretic by lay people more than it is prescribed for this purpose by medical groups.

Preparations.—

Alcohol (Alcohol), U.S.P., contains not less than 92.3 per cent by weight corresponding to 94.9 per cent by volume.

person. Alcohol depresses also the heat-regulating mechanism in the same manner as the antipyretics, and before the advent of the modern antipyretics it was used to reduce temperature.

Small doses (10-25 cc.) in man produce an insignificant increase in the pulse rate, due mainly to the excitement and to the reflex effect on the gastrointestinal tract. Larger doses produce the same effect, but may be followed by lowered blood pressure due to paralysis of the vasoconstrictor centers and weakening of the heart muscle.

Digestion.—Alcohol is one of the few substances which may be absorbed directly from the stomach and intestine. The effect of alcohol upon the function of the digestive organs depends upon the presence or absence of gastrointestinal disease, the degree of alcoholic tolerance, the concentration of the beverage used, as well as the type and amount of food present. Small doses in the patient who likes alcohol will stimulate the secretion of gastric juice rich in acid. Salivary secretion is also reflexly stimulated. Large and concentrated doses of alcohol tend to inhibit secretion and enzyme activity in the stomach, although the effect in the intestine seems to be negligible. However, when large quantities of alcohol are taken over a period of time, gastritis, deficiency conditions, and other untoward results have been observed

TABLE IV

RELATION BETWEEN CLINICAL INDICATIONS OF ALCOHOLIC INTOXICATION AND CONCENTRATION OF ALCOHOL OF THE BLOOD AND URINE

STAGE	% BLOOD ALCOHOL	% URINE ALCOHOL	CLINICAL OBSERVATIONS
Subclinical	0-0.11	0-0.15	Normal by ordinary observation, slight changes detectable by special tests.
Emotional instability	0.09-0.21	0.13-0.29	Decreased inhibitions; emotional instability; slight muscular incoordination; slowing of responses to stimuli.
Confusion	0.18-0.33	0.26-0.45	Disturbance of sensation; decreased pain sense; staggering gait; slurred speech.
Stupor	0.27-0.43	0.36-0.58	Marked decrease in response to stimuli. Muscular incoordination approaching paralysis.
Coma	0.36-0.56	0.48-0.72	Complete unconsciousness; depressed reflexes; subnormal temperature; anesthesia; impairment of circulation; possible death.
Death (uncomplicated)	over 0.44	over 0.60	

Excretion.—Alcohol leaves the body mainly through the kidney and lungs. It produces an increased flow of urine not because of

stomach tube. If one is sure that alcohol alone is causing the intoxication, emptying the stomach may be of little value, but often other intoxications are hidden by the alcohol. Again, the stomach, paralyzed by alcohol or any other cause, is often benefited by cleansing. If the temperature has fallen much, heat in various forms should be applied. As a stimulant to the heart and brain, three to five grain doses of caffeine may be given in the form of hot tea or coffee. This also aids in elimination. Ephedrine and metrazol may also be tried. In case of threatened respiratory failure, artificial respiration, and carbon dioxide and oxygen inhalation, may be beneficial. The patient's position should be changed frequently to combat the development of hypostatic pneumonia.

The headache, nervousness, and gastric irritability, which frequently follow acute alcoholism, are best relieved by a laxative, such as calomel, and by sodium bicarbonate and bismuth subcarbonate. If headache is severe, acetphenetidin may be given. Caffeine in the form of tea or coffee will often relieve headache. Large volumes of fluid may aid in elimination of toxic products. Combined glucose and insulin therapy has also given promising results.

Chronic Alcoholism.—The effects of chronic alcoholism are due first to its local irritant action, which may be manifested on the internal organs after absorption and during excretion; second, to abnormal products of digestion, because of the degenerative changes it produces in the alimentary tract, liver, kidneys, heart, and muscles; third, to the specific action on the central nervous system.

The more common manifestations of chronic alcoholism are: redness of the face, nose and conjunctivae due to the injection of the vessels, gastroenteritis, cirrhotic changes in the liver, nephritis, arteriosclerosis and chronic myocardial changes, amblyopia due to orbital optical neuritis, dulling of the mental faculties, tremors due to nerve degeneration, muscular weakness, and moral deterioration. Not infrequently the prolonged use of alcohol leads to insanity, or the mental change may manifest itself in the gradual weakening of the mental powers, with hallucinations and delusions, or other forms of psychosis.

Delirium tremens is a special manifestation of chronic alcoholism, and usually occurs after continued excess and follows the abstinence from the usual allowance of alcohol. It may be excited or brought on by the absence of food, exposure, hemorrhage, operations, or in any serious illness, especially pneumonia. It is probably due to the sudden withdrawal of the accustomed alcohol, and means simply an

Dehydrated Alcohol (Alcohol Dehydratum, Absolute Alcohol) contains not less than 99 per cent by weight of ethyl alcohol.

Diluted Alcohol (Alcohol Dilutum), U. S. P., contains not less than 41 per cent and not more than 42 per cent by weight of ethyl alcohol.

Whisky (Spiritus Frumenti), N. F. Whisky is an alcoholic liquid obtained by the distillation of the fermented mash of wholly or partly malted cereal grains, and containing not less than 47 per cent and not more than 53 per cent by volume of ethyl alcohol. It must have been stored in charred wood containers for a period of not less than four years.

Brandy (Spiritus Vini Vitis), N. F. Brandy is an alcoholic liquid obtained by the distillation of the fermented juice of sound, ripe grapes and containing not less than 48 per cent and not more than 54 per cent by volume of ethyl alcohol. It must have been stored in wood containers for a period of not less than two years.

Other spirits are solutions of volatile substances in alcohol. In most cases the dissolved substance has a more important action than the alcohol which is used merely as a solvent.

Wines are fermented liquors made from grapes or other fruit juices. Besides alcohol, wines may contain various acids, such as tartaric, tannic, malic, etc.

Dry wines are those that contain no added sugar. They contain about 10 per cent alcohol.

Sweet wines are those to which sugar has been added. They contain about 15 per cent alcohol.

Sparkling wines contain carbon dioxide which makes them effervescent, e.g., champagne, sparkling burgundy, etc.

Red wines are made by fermenting grapes with the skins. They contain 15 to 40 per cent alcohol.

White wines are made from grapes within the skins, or from white grapes.

Symptoms of Acute Alcoholism.—In states of acute intoxication, the patient is stuporous or comatose; the skin is cold and clammy, respirations are noisy and slow, and pupils are dilated or normal. The breath is usually heavy with alcohol fumes. Death may result if the coma is very prolonged or if injury, hypostatic pneumonia, or infection complicates the picture.

Treatment of Acute Alcohol Poisoning.—Emetics in deep narcosis are inactive and worse than useless because they add to the depression. The stomach, therefore, should be emptied and washed with a

Methyl Alcohol (Wood Alcohol)

Methyl alcohol is prepared on a large scale by the destructive distillation of wood. It is also prepared synthetically. It is important in medicine chiefly because many cases of poisoning have arisen from its use. Its actions in general are the same as those of ethyl alcohol, and are excreted mainly on the central nervous system. It seems to have a selective action on the optic nerve, and blindness often follows its use. One dose of about 60 cc. has caused permanent blindness. Many such cases have been reported recently. In repeated doses it is much more toxic than ethyl alcohol. It has been used in proprietary medicines because it is cheaper than ethyl alcohol. Its use, however, should be condemned unhesitatingly.

Isopropyl Alcohol

Isopropyl alcohol is a clear, colorless liquid with a characteristic odor and a bitter taste. It is miscible with water, chloroform, and ether but insoluble in salt solutions. It is a good solvent for creosote and compares favorably with ethyl alcohol in its antiseptic action. It has been recommended for disinfection of the skin and for rubbing compounds and back lotions. Its bacteriocidal effects are said to increase as its concentration approaches 100 per cent. It differs in this respect from ethyl alcohol.

Cannabis Indica (Marihuana)

Cannabis indica consists of the dried flowering tops of an East Indian plant, *Cannabis sativa* Linné. The flowering tops are gathered while the fruit is yet undeveloped and carrying the whole of its natural resin. This resinous principle is known as cannabinol. The plant is grown extensively in different countries for the fiber (hemp) and for the seed.

As the seed forms, the resin content diminishes; therefore, in the East Indies where cannabis is cultivated for the drug action, all staminate plants and flowers are removed in order to increase the resin content.

Cannabis is a very ancient drug having long been used among Oriental peoples. It is also known as marihuana, hashish, and bhang. This age-old intoxicant has been chewed, smoked, or drunk for its psychic effects by people all over the world. Recently attention has been drawn to its increased use in this country, especially among young people, who use it chiefly in the form of cigarettes which are known as "reefers" or "Mary Warners."

excessive nervous reaction due to the lack of the alcohol. There may be premonitory symptoms, such as restlessness, tremor, insomnia, and anorexia.

During the attack there is an excessive tremor, insomnia, delirium, and terrifying hallucinations, such as of snakes and small animals creeping over the individual, etc. Also during the attack there may be a temperature of 102-103° F. Death is a quite frequent outcome, resulting either from pneumonia, traumatism, or collapse.

Treatment of Chronic Alcoholism.—Chronic alcoholism is more often seen in people of subnormal mentality, defective heredity, or psychopathic personality than in the so-called normal individual. Treatment must include re-education and help in making better adjustments to the patient's living conditions. The best results are obtained in a hospital or sanatorium. The alcohol allowed should be reduced gradually, but completely within a week. Proper sedation with belladonna alkaloids, chloral, or paraldehyde is helpful. Careful attention must be given to the adequacy of the diet and the patient's general hygiene. There must, of course, be adequate medical supervision at all times as well as good nursing care. Relapses are rather frequent but less so than with morphine addicts.

Contraindications.—Ethyl alcohol is definitely contraindicated for certain patients and to be avoided in others.

1. Ulceration along the gastrointestinal tract, especially patients with gastric and duodenal ulcer or those with hyperacidity.
2. Acute infection of the genitourinary system.
3. During pregnancy.
4. Epilepsy.
5. Disease of the liver and kidney.
6. People who give evidence of becoming easily addicted.

Alcohol and Life Span.—The effect of alcohol on resistance to infection and life span has been a subject of controversy for many years. It is believed that evidence is lacking to prove that moderate amounts of alcohol have much effect one way or the other. Statistics show, however, that chronic alcoholics and heavy drinkers have a shorter life span than those who abstain from alcohol. Some of the ill effects which have been attributed directly to alcohol have been found to be due to general impairment of health which in turn is due to malnutrition, poor hygiene, etc. Adulteration of ethyl alcohol with methyl alcohol, the presence of impurities and higher alcohols are likewise responsible for distressing symptoms of poisoning. The solution of the social problem involved seems to be a matter of the wise use of alcohol in contrast to its abuse.



PLATE VI—*Cannabis sativa* (Indian Hemp, Marihuana; American Hemp). (Courtesy Parke, Davis & Co)

Cannabis is mentioned in the early Hindoo and Chinese works on medicine. It was used by the Mohammedan sect known as the Hashishin or Assassins (hence the name hashish) who came in contact with the Crusaders in the eleventh and twelfth centuries. It is a sedative and hypnotic, but is a strongly habit-forming drug. Not an important drug.

Actions.—An interesting description of its action on himself is given by H. C. Wood, Sr., in his *Therapeutics, Its Principles and Practice*. These actions, however, are hard to elicit in most people.

The main actions are depression of the higher centers with mental exhilaration associated with hallucinations, due to disordered consciousness of time, locality, and personality, unbridled imagination resulting in a dreamy state resembling that effected by morphine. The sensations of pain and touch are lessened, the extremities feel numb, and a state of indifference to surrounding influences comes on. Before sleep is induced there is often more or less general hyperesthesia. One must wonder how accurate is the description of such conditions when carried out subjectively.

Unlike morphine, cannabis produces ataxia while the respiratory and circulatory systems are but little influenced, and although alarming symptoms may follow its use, no deaths have been reported.

Although violent acts have been performed while under the influence of the drug, they are probably due to the lifting of a normal restraining influence on the personality which already has psychopathic tendencies.

Habituation and Tolerance.—The drug is habit-forming and habituation does occur, but true addiction does not develop to the extent that there are withdrawal symptoms. The prolonged use of the drug, especially in the young and immature individual, is likely to lead to deterioration. Its use is learned as an escape mechanism which is unhealthy in every sense of the word.

The Federal government has taken steps not only to regulate the sale of this drug but also to control its cultivation. The latter is especially difficult because it grows easily and almost everywhere.

Therapeutics.—Owing to its tendency to deteriorate and the great difference in individual susceptibility, cannabis is very little employed and cannot be recommended. It is mentioned here largely because of its social implication. There are no official preparations.

Questions for Review and Suggestions for Study

1. In what ways may drugs affect the central nervous system?
2. In general, what are the expected results of such action?
3. What is the nature of the action of opium on the central nervous system?
4. What are the chief alkaloids of opium?
5. How do they differ in their action and how do their uses depend upon these differences in action?
6. a. How do morphine and aspirin differ in their method of relieving pain?
b. What is the most dangerous symptom to watch for after a patient receives morphine? Explain.
7. Contrast the action of strychnine and caffeine on the central nervous system.

8. Why is a cup of coffee sometimes beneficial just before writing an examination?
9. How would you explain that the chief use of strychnine is for its tonic effect?
10. What are some of the indications of idiosyncrasy to morphine which patients may exhibit?
11. What will you do if a patient tells you that he is sensitive to morphine and the doctor has left a written order for the patient to receive a dose of this drug?
12. What can you as a nurse do to minimize the danger of habit formation in relation to the habit-forming drugs?
13. What signs or symptoms would lead you to suspect that a patient is addicted to the use of opium in some form?
14. Why is it particularly dangerous for a nurse to take hypnotics or analgesics on her own responsibility?
15. What is the site of action of the coal tar analgesics?
16. How does an analgesic differ from an anodyne?
17. What are some of the possible causes for headache? What can you do to help relieve a headache without resorting to the use of drugs?
18. What symptoms of poisoning will you watch for when a patient is receiving cinchophen?
19. Why has the use of cannabis indica become a problem of increasing social significance? Discuss.
20. Under what conditions might you expect bromides to be ordered in preference to barbiturates or coal tar analgesics?
21. Why is it essential for you to notice the early symptoms of overdosage of drugs such as bromides?
22. Why is caffeine sodium benzoate frequently given in preference to the alkaloid caffeine?
23. List the various anesthetics which are used in your hospital. How does the choice of anesthetic influence the specific nursing care and what precautions are you expected to observe?
24. List the hypnotic drugs which are given in your hospital and make a study of those which you had an opportunity to observe in your patients. Tabulate your observations under the following suggested headings:
 Name of patient _____
 Name of drug _____
 Purpose for which given _____
 Expected action _____
 Expected result _____
 Results actually observed _____
 General remarks _____
25. Make a list of the opium preparations given to your patients during the course of three or four days. Why was each drug ordered for a particular patient? Were the expected results obtained? How long a time elapsed before the drug began to be effective? What factors influenced the length of time before you could observe the results of action? Did you observe any signs of idiosyncrasy? If so, what were they? What was the usual method of administration?
26. What is the systemic action of ethyl alcohol? What are its therapeutic uses? Why is chronic alcoholism essentially a problem for the psychiatrist?



CHAPTER XII

DRUGS WHICH AFFECT THE AUTONOMIC NERVOUS SYSTEM

THE AUTONOMIC NERVOUS SYSTEM

Autonomic (*autos*, self + *nomus*, law) means a law unto itself, or self-governing. It controls the functions of all tissues except the striated muscles. It has been called by other names. Winslow (1732) called it sympathetic because he thought it controlled the sympathies of the body; Bichat (1800) called it vegetative to designate its control over the nutrition, as opposed to animalic processes. Gaskell called it the involuntary nervous system to contrast it with the voluntary which controls skeletal movement. While it is autonomic, we have but slight control over it. It consists of nerves, ganglia, and plexuses which regulate the heart, the smooth muscle of the body, and the glands. Thus respiration, digestion, circulation, metabolism, sweating, and the secretion of some of the endocrine glands are regulated by this system. It is ordinarily divided into the sympathetic and the parasympathetic divisions (see Plate VII).

Differences Between the Sympathetic and Parasympathetic Divisions

While anatomic and physiologic differences do exist between the sympathetic and parasympathetic divisions, these differences are not as clear-cut and absolute as might be supposed. One of the differences lies in the fact that sympathetic nerve fibers ramify to a much greater extent than do the parasympathetic fibers. A preganglionic nerve fiber may not only pass through a number of ganglia in the sympathetic chain but it also frequently synapses with a large number of postganglionic fibers. In this way the sympathetic system may accomplish mass action through diffuse discharge of nerve impulses. The parasympathetic nervous system in contrast has its ganglia close to the organ which it innervates and thus is more limited in the discharge of its nerve impulses. On the other hand, the parasympathetic is more essential to life. The sympathetic is geared for mass response and the expenditure of large amounts of

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ympathetic

Parasympathetic

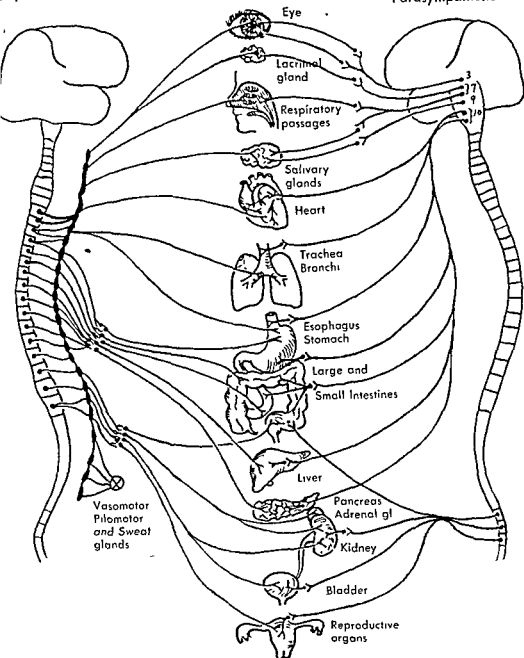


PLATE VII.—Diagram of the autonomic nervous system. The craniosacral (parasympathetic) division is shown in green. The thoracolumbar (sympathetic) division is shown in red.

energy. The parasympathetic is concerned with functions of conservation and restoration. In general if one system stimulates a function the other system inhibits that function. Viscera are usually innervated by both divisions. The action of one system may be made prominent by the blocking of effects in the opposing system.

Chemical Theories of Nerve Impulses

Evidence has been brought to bear to substantiate the theory that conduction of nerve impulses at the synaptic connections and at the myoneural junctions is brought about by chemical mediators. In the parasympathetic system this substance is known as acetylcholine. In the sympathetic division it is called sympathin. It is thought that acetylcholine exists in the tissues in an inactive form and is made active by the passage of nerve impulses. It is subject to inactivation by an enzyme also present in the tissues, called cholinesterase. This enzyme is capable of changing acetylcholine to choline and acetic acid. The action is rapid, hence the action of acetylcholine when it is released by nerve impulses is brief. When the enzyme is inactivated, the action of acetylcholine is intensified and prolonged.

The theory that two chemical mediators explain fully nerve impulses is not without question. On the bladder, there are two parasympathetic responses: (a) a tonic response caused by acetylcholine is abolished by atropine; (b) a rapid contractile response is not influenced by atropine. Some actions on the intestine are also resistant to atropine. Dale has suggested that in such cases the nerve impulses liberate acetylcholine so close to the relative structures that atropine cannot intervene, whereas if the acetylcholine is applied from without, atropine can act.

Adrenergic and Cholinergic Drugs

When drugs augment the effects of sympathetic nerve innervation they are said to be sympathomimetic. Those which augment the parasympathetic impulses are called parasympathomimetic. In 1914 Dale found that acetylcholine mimics the action of the parasympathetic nerve impulses much as adrenalin mimics the action of the sympathetic nerve impulses. He suggested the terms cholinergic for drugs which act on the parasympathetic system apparently through liberation of acetylcholine and adrenergic for those that act on the sympathetic, apparently through the liberation of epinephrine.

Site of Drug Action

Autonomic drugs act upon the effector cells rather than on the nerve endings. They may make the cells more or less sensitive to the chemical mediator or they may inhibit the action of the enzyme which normally destroys the mediator. For example, it is believed that physostigmine exerts its action on cholinesterase to the extent that it inhibits its action and thus prolongs the effect of acetylcholine on the effector cells.

DRUGS ACTING ON STRUCTURES SUPPLIED WITH ADRENERGIC NERVES

Epinephrine (Adrenalin)

Source and General Characteristics.—Epinephrine is a hormone produced in the medullary portion of the adrenal gland and its action greatly resembles that resulting from stimulation of the sympathetic nervous system. Because it mimics the action of the sympathetics, Barger and Dale suggest the term sympath-o-mimetic, to describe its action. (Mimetic < Gr. *mimetikos*, to mimic or to imitate.) It is commercially obtained from the adrenal glands of sheep, cattle, and hogs. It has also been prepared synthetically.

Pharmacologic Action.—

A. Local.—Epinephrine has no effect upon the skin but when applied to mucous membrane, wounds, or when injected into tissues, it produces a very rapid vasoconstriction which may last as long as two hours.

B. Systemic.—Epinephrine acts upon the effector cells (muscle and gland cells) connected with the sympathetic nervous system. It is believed to be the same as sympathin. For the most part, its action is the same as that resulting from stimulation of the sympathetic nerve to the part acted upon. If stimulation of the part causes contraction of the muscle, epinephrine causes contraction. If stimulation causes relaxation, epinephrine causes relaxation. An exception exists in the response of the sweat glands and the pilomotor muscles, neither of which are affected in the human being, although there is increased sweating in many of the animals and also pilomotor activity. Mydriasis is not secured after therapeutic doses of epinephrine except under special conditions. *Epinephrine exerts its main action upon the heart, the blood vessels, and some of the smooth muscle of the body.*



Intestinal tone is decreased and peristalsis is diminished. The emptying time of these organs would thus be increased. However, therapeutic doses of this drug rarely produce these effects.

Epinephrine stimulates the musculature of the splenic capsule, thereby increasing contractions of that organ. This action results in increasing the number of red cells and the viscosity of the blood.

Action on the Glands.—The glandular action of epinephrine is relatively unimportant. Its action on the salivary gland resembles the effect of stimulation of the sympathetic nerve, i.e., the secretion obtained is of the sympathetic type—thick and rich in organic matter. Little or no effect is seen on the glands along the rest of the digestive tube with the exception of the liver. Epinephrine causes glycogenolysis and a rise in the blood sugar. This effect is sometimes utilized in the treatment of insulin shock if there is reason to believe the glycogen stores are normal.

The action of epinephrine on the human uterus does not seem to have any therapeutic significance.

Absorption and Excretion.—Although epinephrine is readily absorbed from mucous membranes, it is destroyed by digestive enzymes and cannot be given by mouth. Rapid effects may be noted when the drug is given hypodermically or intramuscularly and almost immediate effects occur when it is given intravenously. The drug is rapidly excreted.

Therapeutic Uses.—

1. An important use of epinephrine is to constrict blood vessels by local application. It can be used to diminish hyperemia of the conjunctiva, to reduce congestion in nasal membranes and to check or reduce hemorrhage of mucous membrane in surgery of the eye, ear, nose, mouth, or throat. Epinephrine is effective only in checking bleeding of the smaller arterioles or capillaries; it has no value in controlling hemorrhage from larger vessels.

2. Epinephrine is probably the most valuable drug for the treatment of acute bronchial asthma. The subcutaneous administration of 0.2 to 0.3 cc. of a 1:1000 solution provides rapid relief. Dosage may be repeated hourly if necessary. It is likewise of great value to relieve the acute symptoms of allergic conditions seen in serum reactions, angioneurotic edema, hay fever, urticaria, etc. Dose: 0.3-0.5 cc. of a 1:1000 solution.

3. Epinephrine enhances the action of local anesthetics when given with them by constricting the blood vessels in the field of operation

THE HEART.—Epinephrine accelerates the heart rate by stimulating the myocardium and the conduction tissue.¹ This results in stronger contraction and a more complete emptying of the chambers and usually a prompt rise in blood pressure. After a short time the increase of blood pressure reflexly slows the heart by stimulation of the vagus center. Small doses accelerate and strengthen the heart. Large doses may cause so great an acceleration that efficiency is temporarily lessened, and if the heart muscle is weak, as may be true in disease or when certain drug effects are present, it may strain it sufficiently to cause acute dilatation, disturbances in rhythm, or ventricular fibrillation.

BLOOD VESSELS.—Epinephrine acts chiefly on the smooth muscle of the arterioles and to a lesser extent on the capillaries and veins. It stimulates the smooth muscle in the vascular beds in the same way as the sympathetic nervous system does. The blood vessels in the skeletal muscles are relaxed; the skin vessels and those in the viscera are constricted. This mechanism is of course the one which helps to provide adequate blood in the skeletal muscle to meet a physical emergency. The cerebral vessels and those in the eye and to some extent those in the lungs also constrict. The coronary vessels are usually relaxed, thus increasing the coronary blood flow. The response of given blood vessels, however, is not always identical and appears to be related to the existing state of tonus at the time the drug is administered, i.e., if vessels are constricted, epinephrine may cause dilatation.

The most striking response to the administration of adrenalin when given intravenously is a dramatic rise in blood pressure. Subcutaneous injection results in a slower rise in pressure. *Epinephrine is the most powerful vasoconstrictor known.* When the blood pressure subsides, it lowers to a brief period of hypotension, before it becomes normal. This explains the period of nasal congestion which occurs after the use of epinephrine in nasal drops and sprays.

SMOOTH MUSCLE.—Epinephrine relaxes the smooth muscles in the respiratory tract, especially if they are hypertonic. The action, which is immediate and very effective, relieves bronchial constriction, as seen in acute asthma.

The smooth muscle of the stomach and intestines is relaxed by large doses of epinephrine, and the sphincters are usually contracted, although the sphincter action depends on the state of tonus

¹Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 403.

tract. The subcutaneous route is the one most often employed. The intravenous route is rarely used but if employed the drug must be given very slowly and in a very low concentration. Epinephrine in oil preparations is usually given intramuscularly. Epinephrine may be given by inhalation in the form of nasal sprays.

Preparations.—

Epinephrine Solution (Liquor Epinephrinae), U. S. P., Solution 1:1000 (aqueous). Dosage: 0.06-1.0 cc. (1 to 15 minims). Given locally.

Epinephrine Injection (Injectio Epinephrinae), U. S. P., 1:1000 solution in ampule form. Dosage: 1 mg. ($\frac{1}{60}$ grain) subcutaneously or intramuscularly.

Epinephrine Inhalation (Inhalatio Epinephrinae), U. S. P., Solution of Epinephrine Hydrochloride 1:100.

Suspension of Epinephrine in Oil 1:500, N. N. R. Dose: 0.2-1½ cc. (3-22 minims) intramuscularly.

Solutions of epinephrine do not keep well; deterioration is evidenced by formation of sediment and brownish discoloration.

Symptoms of Poisoning.—Mild symptoms of poisoning are most often seen in nervous patients, those with hypertension or exophthalmic goiter. Symptoms usually consist of increased nervousness, muscular tremor, pallor, anxiety, headache, palpitation, respiratory difficulty, and precordial pain.

More dangerous effects may result from large doses or when the drug is given intravenously. These include cardiac dilatation, pulmonary edema, and cerebral accident. Death may also result from ventricular fibrillation.

The milder symptoms usually disappear with rest, reassurance and discontinuance of the medication. The more serious symptoms must be treated symptomatically. They are best avoided by cautious use of the drug. Epinephrine should be avoided in patients with heart disease, hyperthyroidism, and nervous instability. Gormsen* reports a death following the subcutaneous injection of 60 mg. of epinephrine, given by mistake. A 10 per cent solution for use by inhalation was used. Death resulted in a few minutes. The symptoms were immediate pain in the neck, anxiety, pallor, vomiting, dyspnea, increased pulse rate, marked rise in blood pressure, and collapse. Necropsy showed hyperemia of all organs, but neither macroscopic nor microscopic changes were specific.

*Abst. A. M. A. 112: 2644, 1939.

and thereby checking bleeding, preventing widespread absorption of the anesthetic, and intensifying the anesthetic in the region where it is needed.

4. In heart block 0.3 to 0.5 cc. of a 1:1000 solution may be given subcutaneously if fainting attacks occur.

5. Acute heart failure—Epinephrine is a powerful drug and requires great caution when used as a heart stimulant. In certain conditions of heart failure 0.25-0.5 cc. of a 1:1000 solution is given subcutaneously or occasionally very small amounts are added to in-

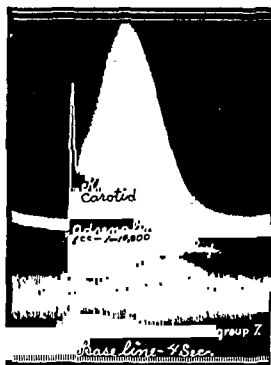


Fig. 15.—Blood pressure and respiration showing the effects of intravenous injection of adrenalin. (From Jackson: *Experimental Pharmacology and Materia Medica*.)

travenous fluids. If too much epinephrine is given when the heart is in a weakened condition, ventricular fibrillation and death may result. Cases have been reported in which patients have been brought back to life after the heart has stopped beating for several minutes by injecting directly into the heart or into veins close to the heart and by massaging the organ in such a way that the epinephrine circulates through it. Intracardiac injection should be used only as a last resort.

Administration.—Epinephrine is given either locally or parenterally. When given orally it is destroyed by enzymes in the digestive

tract. The subcutaneous route is the one most often employed. The intravenous route is rarely used but if employed the drug must be given very slowly and in a very low concentration. Epinephrine in oil preparations is usually given intramuscularly. Epinephrine may be given by inhalation in the form of nasal sprays.

Preparations.—

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Epinephrine Injection (Injectio Epinephrinae), U. S. P., 1:1000 solution in ampule form. Dosage: 1 mg. ($\frac{1}{60}$ grain) subcutaneously or intramuscularly.

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*Abst. A. M. A. 112: 2644, 1939.

Twenty-eight deaths previously have been reported. The minimum fatal dose of epinephrine subcutaneously seems to be about 10 mg

Ephedrine, U. S. P.

Ephedrine is the name given to an active principle isolated from an Asiatic drug, ma huang (*Ephedra vulgaris* var. *helvetica*), which has been used in the practice of medicine in China for more than five thousand years. In chemical composition it is closely allied to epinephrine.

Ephedrine is a sympathomimetic drug which greatly resembles epinephrine but, in addition, it stimulates the central nervous system. It differs from epinephrine in a number of ways. It can be given not only parenterally but also orally because it is absorbed from the gastrointestinal tract. Ephedrine has a more prolonged action on the heart and blood vessels, although its action is slower and weaker. Vasodilation does not ordinarily follow vasoconstriction as may occur after epinephrine. The central action of the drug is exerted mainly on the cortex and medulla. It acts as a mydriatic in the eye.

Ephedrine relaxes hypertonic muscle in the bronchial tubes and in the gastrointestinal tract. Emptying time of the stomach and intestine is delayed. Sphincter muscles in the urinary as well as in the gastrointestinal tracts are stimulated. The effect on metabolism is similar to that of epinephrine.

Therapeutic Uses.—

1. Ephedrine is used to combat low blood pressure after spinal anesthesia as well as in certain other hypotensive states.

2. In the treatment of bronchial asthma, ephedrine is useful in preventing acute attacks. Epinephrine is preferable when attacks are acute because of its more rapid action.

3. As a constituent of nasal drops, jellies, and sprays ephedrine relieves acute congestion of hay fever, sinusitis, head colds, and vasomotor rhinitis. Shrinkage of mucous membranes begins immediately and lasts for several hours.

4. Ephedrine is also effective for the treatment of narcotic poisoning. It stimulates the respiratory center as well as the cerebral cortex. It has also been used in treatment of narcolepsy, a state in which the patient persistently falls off to sleep.

5. In the treatment of muscle weakness associated with myasthenia gravis. It is most effective, however, when combined with prostigmine.¹

¹Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, The Macmillan Co. p. 434.

6. Ephedrine may be used in solution as a mydriatic when a cycloplegic action is not necessarily desired.

Dosage.—Salts of ephedrine are effective whether given orally, intramuscularly, or intravenously. As a spray it is used in 0.5 to 2 per cent solution of a salt of ephedrine. In ophthalmologic work it is used in 4 per cent solution. Orally the dose is from 20 to 50 mg. ($\frac{1}{2}$ to $\frac{5}{8}$ gr.) every three or four hours.

Preparations.—

Ephedrine (Ephedrina), U. S. P. No dosage specified. Rather insoluble in water.

Ephedrine Hydrochloride (Ephedrinae Hydrochloridum), U. S. P.; Dosage: 0.025 Gm. ($\frac{3}{8}$ gr.).

Ephedrine Sulfate (Ephedrinae Sulfas), U. S. P. Dosage: 0.025 Gm. ($\frac{3}{8}$ gr.).

Jelly of Ephedrine Sulfate (Gelatum Ephedrinae Sulfatis), N. F.

Ephedrine Spray (Nebula Ephedrinae), N. F.

Symptoms of Poisoning.—Toxic doses are likely to cause insomnia, nervousness, dizziness, tremor, headache, heart palpitation and sweating. Sometimes nausea and vomiting and precordial pain are reported. The same precautions should be observed in the use of ephedrine as are essential with epinephrine. Barbiturates or some type of sedative may be desirable when a patient is getting ephedrine over a period of time, to avoid undue central stimulation.

Phenylephrine (Neo-Synephrine Hydrochloride) N. N. R.

Phenylephrine is a synthetic vasoconstrictor drug which is chemically related to epinephrine and ephedrine. It may be administered orally. When applied to mucous membranes it constricts small blood vessels and reduces congestion. It is valuable in the treatment of sinusitis, vasomotor rhinitis, and hay fever. For topical application to mucous membranes the 0.25 per cent solution is ordinarily used.¹

Like ephedrine and epinephrine it is also used to combat hypotension in spinal anesthesia and to intensify the anesthesia of a local anesthetic. For parenteral injection 0.1-1 cc. of a 1 per cent solution is used.

Propadrine Hydrochloride, N. N. R.

Propadrine hydrochloride acts similarly to ephedrine. When applied locally in the form of a 1 per cent aqueous solution or 0.66

¹N. N. R., 1947, p. 226.

per cent jelly, it produces constriction of the capillaries, thereby shrinking swollen mucous membranes. It is said that its action is somewhat more prolonged than that of ephedrine. It is also claimed that the anxiety complex is not so likely to ensue with propadrine hydrochloride as with ephedrine.¹

Dosage.—As a spray or installation, 1 per cent aqueous solution or application of 0.66 per cent jelly locally; orally a three-eighths grain capsule every two to four hours as indicated.

Amphetamine (Benzedrine)

Amphetamine is a sympathomimetic amine which exerts an action similar to that of epinephrine and ephedrine in that it acts as a stimulant to parts supplied by adrenergic nerves. It causes elevation of blood pressure, increased heart action, relaxation of the gastrointestinal muscle, and dilation of the pupil. In addition, it stimulates the brain stem and cerebral cortex (see preceding chapter). As a 1 per cent solution in liquid petrolatum it may be sprayed on the nasal mucous membrane. It relieves congestion of the mucosa in the treatment of colds, hay fever, vasomotor rhinitis, etc. Its overuse as an inhalant should be avoided because of its systemic effects

DRUGS WHICH ACT CHIEFLY ON STRUCTURES SUPPLIED BY CHOLINERGIC NERVES

The Atropine or Belladonna Group

The atropine or belladonna group includes belladonna (deadly nightshade),² stramonium (jimson weed or thornapple),³ scopolia, and hyoscyamine (henbane).⁴ The chief alkaloids of these plants are atropine, hyoscyamine, and hyoscyne or scopolamine.

Atropine seldom occurs in the plant except in traces in the young leaves and shoots. Hyoscyamine is found in the older plants and roots and in the process of extraction is changed to atropine.

¹N. N. R. 1944, p. 288.

²Name of *Atropa belladonna* from Greek and Roman Mythology.

THREE FATES

CONTROLLED THE DESTINIES, HUMAN AND DIVINE

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⁴Henbane is thought to be a corruption of henne-bell, which suggests a musical instrument. In mediaeval Latin, henbane was referred to as *Symphoniaca Herba*; *Symphoniaca* being a rod with many bells on it. (Wootton)

Henbane is the bane of domestic fowl.



PLATE VIII—*Atropa belladonna* (Deadly nightshade). (From Jackson.
Experimental Pharmacology and Materia Medica.)

Hyoscine or *scopolamine*, $C_{17}H_{21}NO_4$, formerly thought to be an isomer of atropine, differs slightly from atropine in its formula. It decomposes into tropic acid and scopoline (oscine), which is closely related to tropine.

These alkaloids resemble each other closely in the effects produced by them in animals and man.

ATROPINE

Atropine is the chief alkaloid of the plant *Atropa belladonna* which is grown for commercial purposes in Germany and England, Austria and America.

A. Local Action.—

On the Skin.—There is a slight amount of absorption when the drug is applied to the skin, especially in oily or alcoholic preparations or in the form of plasters containing the whole drug. Belladonna ointment or suppositories may be used on mucous surfaces. Its local effect for the relief of pain is slight, however, and is accomplished by depression of sensory nerves.

On the Eye.—Aqueous or oily solutions of atropine when introduced into the eye produce dilation of the pupil, diminished secretion of tears, impaired ability to focus objects near at hand, and increased tension inside the eyeball. (Further discussed in chapter on Pharmacology of the Eye, p. 376.)

B. Central Action.—

On the Cerebrum.—Small or moderate doses have no appreciable effect on the cerebrum. Following toxic doses, the patient may become restless, wakeful, and talkative, a condition which may develop into a delirious state and finally into stupor and coma. During the exalted, excited period the patient may be described as having a "belladonna jag." A rise in temperature may result from stimulation of the heat-regulating center.

On the Medulla.—In small or moderate doses, atropine stimulates the respiratory center in the medulla and makes breathing faster and deeper. Large doses, however, cause respiratory paralysis, so that the dose must be calculated with care.

Small doses stimulate the vagus center, causing primary slowing of the heart. The vasoconstrictor center is stimulated briefly and then depressed. Because depression follows rather soon after stimulation, atropine is sometimes called a borderline stimulant of the nervous system.

On the Spinal Cord.—Large doses may produce an increased excitability of the cord to the extent that twitching of muscles occurs.

C. Peripheral Action.—The main therapeutic uses of atropine are due to its peripheral action rather than to its central one. This more important action is upon the smooth muscle and secretory glands which are supplied by postganglionic cholinergic nerves. The chief action of atropine then is to make the nerve stimuli of the parasympathetic nerves ineffective by making the tissues which they supply insensitive to acetylcholine.* In other words it *paralyzes the effect of the parasympathetic nerves*. In a broad sense, the action of atropine simulates the overactivity of the sympathetic nervous system.

RESULTS OF PERIPHERAL ACTION.—

1. *In the Eye.*—Dilation of the pupil and paralysis of the muscle of accommodation.

2. *In the Respiratory Tract.*—Decreased secretion of the nose, pharynx, and bronchi. This is particularly true if preceded by excessive secretion. The muscles of the bronchi relax which tends to increase ease of breathing.

3. *In the Heart and Blood Vessels.*—The cardiac rate is at first slowed slightly because of the central action but moderate to large doses rather quickly result in accelerated heart action. There is no striking effect on blood pressure although in large doses, there may be an active vasodilation of the blood vessels of the skin of the face and neck. The mechanism of this vascular response is not clearly understood.

4. *In Glands.*—

(a) **Sweat glands:** The administration of atropine results in decreased perspiration. The skin becomes hot and dry after large doses. This effect is sometimes seen in children who may have a marked elevation of temperature. Suppression of sweating plus the possible effect on the heat-regulating center are causative factors.

(b) **Glands of the gastrointestinal tract:**

- (1) **Mouth:** The saliva and mucous secretions are lessened, the throat and mouth become dry, and the patient may experience marked thirst and difficulty in swallowing.
- (2) **Stomach:** Although some difference of opinion exists among authorities as to the effect of atropine on the

*Bastedo *Materia Medica, Pharmacology and Therapeutics*, p. 498

activity of gastric glands, it appears that the amount and character of the gastric secretion are little affected by atropine, at least when it is given in ordinary therapeutic doses. Effects which are produced in laboratory animals have not always been confirmed in human tissues. The secretion of acid in the stomach is presumably less under vagal control than under hormonal and chemical control.*

- (3) Pancreatic and intestinal glands: there are no effects of therapeutic significance.

5. *Smooth Muscle*.—

- (a) Along the gastrointestinal tract: Gastrointestinal motility, particularly that of muscle tone and peristalsis, is decreased by the belladonna alkaloids. Decrease of muscle activity is more noticeable when conditions of hypermotility and spasm have been present.
- (b) Ureter: Atropine and other belladonna alkaloids exert a relaxing effect, especially when the ureter has been in a state of spasm.
- (c) Gall bladder and bile ducts: A mild antispasmodic effect is noted in these organs.
- (d) Urinary bladder: Atropine produces some degree of relaxation in hypertonic muscle.
- (e) Uterus: The power of atropine to decrease activity of uterine muscle is questionable and at best mildly antispasmodic.

D. Uses and Administration.—Belladonna or its alkaloids may be used in one or more of the following:

1. Locally to relieve pain. They are used in the form of belladonna plasters or ointments, although their value has come to be questioned.
2. To check excessive secretion of saliva in ptyalism and in cases of surgery of the mouth or throat.
3. To treat coryza and to lessen nasal congestion. Rhinitis tablets, which are sometimes prescribed for the relief of early stages of head cold, may contain some atropine.
4. To check perspiration, as in the case of patients with pulmonary tuberculosis.
5. To treat certain eye conditions and for its use as a mydriatic and cycloplegic in eye examinations

*Goodman and Gilman: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 466

6. As a heart and respiratory stimulant, atropine is frequently given with morphine in a preanesthetic hypodermic injection to lessen the effect of morphine on respiration, to stimulate respiration, and to decrease the secretion of mucus in the respiratory passages.

7. To check spasms of involuntary muscles. It may be given with cathartics to lessen griping; to relieve bronchial spasm; for renal and gall bladder colic, to relieve symptoms associated with hypermotility of the stomach and intestine, and for its antispasmodic effect in urinary tract disorders.

Atropine may be given by mouth or hypodermically. For the effect on the stomach, the drug should be given in solution about 15 minutes before the meal. For the relief of night-sweats it is given at bedtime. The average dose of atropine is 0.5 mg. ($\frac{1}{120}$ grain) but since this amount produces unpleasant symptoms in some people, it is advisable to begin with half this dose, 0.25 mg. ($\frac{1}{250}$ grain), and repeat it every two hours until the desired results are achieved. In cases of pylorospasm of infants, atropine may be injected hypodermically or given in food in doses of 0.05 mg. to 0.1 mg. ($\frac{1}{1200}$ to $\frac{1}{600}$ grain). To cause dilatation of the pupil and other local effects on the eye, a solution of atropine is dropped into the conjunctival sac.

E. Some Official Preparations and Dosages:

Belladonna Extract (Extractum Belladonnae), U. S. P. Prepared from the belladonna leaf and contains the alkaloids of the belladonna leaf. Dosage: 15 mg. ($\frac{1}{4}$ grain).

Belladonna Ointment (Unguentum Belladonnae), U. S. P. It is applied locally. Pilular extract of belladonna 10 per cent in dilute alcohol and yellow ointment.

Tincture of Belladonna (Tinctura Belladonnae), U. S. P. Dosage: 0.6 cc. (10 minims). Maximum dose 15 minims.

Atropine Sulfate (Atropinae Sulfas), U. S. P. Dosage: 0.5 mg ($\frac{1}{120}$ gr.) orally or subcutaneously. Maximum dose: gr. $\frac{1}{60}$.

F. Atropine Poisoning.—When atropine is being administered, one should watch carefully for toxic symptoms, the first indications of which are usually dryness of the throat and dimness of vision. A rash may appear, especially over the face, neck, and upper part of the trunk. This is more likely to occur in children, although it may occur in adults. The body temperature in infants may reach an alarming height of 107° F., and more. Even when the drug is being administered as an eye lotion, sufficient absorption may take place to produce general symptoms and even to cause such toxic effects as rapid pulse, flushing of the skin, delirium, marked dilatation of

the pupils, elevation of the temperature, and dryness of the throat and skin. This is followed more or less quickly by unconsciousness, prostration, and death from paralysis of the respiration, following stimulation.

G. Treatment.—If the drug has been taken by mouth, the stomach should be washed out promptly and tannic acid or tea given as an antidote. The patient should be catheterized to prevent reabsorption of atropine from the urine, and stimulants such as caffeine or strychnine administered if depression is present. Artificial respiration may be given if necessary, and the administration of carbon dioxide and oxygen may be useful. Remaining therapy and nursing care are largely symptomatic. Icecaps to the head during the stage of excitement, cold sponges to reduce temperature and possibly one of the rapid-acting barbiturates may be ordered.

SYNTHETIC ALKALOIDS RELATED TO ATROPINE

1. Homatropine.—HOMATROPINE HYDROBROMIDE, U. S. P., is an artificial alkaloid of atropine. The actions of homatropine are nearly identical with those of atropine, except that the dilatation of the pupil caused by it occurs more promptly and disappears more rapidly. Its local use in the eye is not so likely to cause general symptoms; for instance, the throat does not become dry as it does after atropine. The mydriatic effect of homatropine is increased by adding cocaine to it. The dose is 0.5 mg. ($\frac{1}{120}$ grain). Homatropine is used chiefly as a mydriatic in place of atropine. It may be employed in a 2 per cent aqueous solution or 5 drops of a 1 in 500 solution may be introduced into the conjunctival sac, one drop at a time, at intervals of five minutes. This method will produce complete dilatation in three-quarters of an hour.

Homatropine Hydrochloride, N. N. R., is given for the same indications as the hydrobromide. It is applied to the eye in 1 per cent solution.

HOMATROPINE METHYLBROMIDE, N. F. (NOVATRINE)

A synthetic alkaloid which is said to be less active than atropine on the central nervous system. Its uses for disorders of the gastrointestinal tract are similar to those of atropine. Novatropine is made up for oral use in 2.5 mg. tablets. The dose is two tablets, two or three times daily.

2. Syntropan, N. N. R.—A synthetic alkaloid, which is also similar in its action to atropine, is used chiefly for its antispasmodic effect in gastrointestinal spasm, dysmenorrhea, and for ureteral and bladder spasm. It has, in addition to its inhibitory effect on parasympa-

thetic nerve impulses, a direct action on smooth muscle. This drug is prepared in tablets of 50 mg. for oral use and in ampule form of 10 mg. each for subcutaneous and intramuscular injection.

4. **Trasēntin.**—A nonofficial synthetic alkaloid which exhibits a highly selective action on smooth muscle but lacks the mydriatic, cardiac, and glandular effects of atropine. It is used for its antispasmodic effects for the same gastrointestinal disorders for which atropine may be used.* The drug is marketed for oral use in 75 mg. tablets and in 1.5 cc. ampules for hypodermic administration.

OTHER DRUGS OF THE BELLADONNA GROUP

1. **Scopolamine or Hyoscine.**—Scopolamine resembles atropine in its effects upon the nerve endings but differs from it in having a depressant rather than a stimulating effect on the brain. It does not increase the respiration to any extent and it slows the heart. It is used as a cerebral sedative in many forms of insanity, such as delirium, mania, delirium tremens, etc., but its use for such purposes is dangerous, since even in small doses it sometimes causes a rapid fall in blood pressure, and collapse.

Morphine and scopolamine form a desirable preanesthetic combination for local and spinal anesthesia. They quiet the patient, allay fear and apprehension, and reduce shock to the nervous system. It has frequently been employed to produce the partial anesthesia commonly known as twilight sleep, but the effects on the child are too uncertain, many children being born dead or asphyxiated. Scopolamine is frequently used as a mydriatic. Its effects appear more promptly and disappear more rapidly than those of atropine and it is not so irritating. For these reasons it is often preferred to atropine.

Preparation.—

Scopolamine Hydrobromide (*Scopolaminae Hydrobromidum*), U. S. P.
Dosage: 0.0005 Gm. ($\frac{1}{120}$ gr.).

2. **Hyoscyamus and Hyoscyamine.**—Hyoscyamine, while it closely resembles atropine in its central action, has an effect about twice as strong in its peripheral action. Hyoscyamus, U. S. P., contains not only hyoscyamine but also atropine and hyoscine. It is sometimes ordered for hypertonic conditions of the bladder and urethral sphincter, and in cystitis. Since it is difficult to obtain hyoscyamine in a pure form, it is rarely used in therapeutics. **Tincture of Hyoscyamus**, U. S. P.; 2-4 cc.

*Goodman and Gilman: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 471.

3. **Stramonium.**—Stramonium, U. S. P., consists of the dried leaves and flowering tops of the *Datura stramonium*, a weed which grows in England and in the United States. Stramonium leaves as such or in the form of cigarettes are burned and the fumes inhaled to relieve the attacks of asthma. Stramonium ointment is used as an anodyne in cases of painful hemorrhoids.

The official preparations are:

Tincture of Stramonium, U. S. P. Average dose 0.75 cc. (12 minims).

Extract of Stramonium, U. S. P. Average dose 20 mg. ($\frac{1}{3}$ grain).

Parasympathomimetic Agents

As mentioned at the beginning of this chapter, the role of acetylcholine is believed to be that of a chemical mediator between the parasympathetic nerve endings and the effector cells. Therefore when this substance is given parenterally, it intensifies the action of this branch of the autonomic nervous system. Its effects, however, are too transitory to be of therapeutic value since it is so rapidly destroyed in living tissues. An effort was made to find a related compound which would be more stable but have much the same effect. Other esters of choline have now been synthesized: acetyl-beta-methylcholine (mecholyl) and carbaminoylcholine (doryl). Clinically these two drugs are similar but differ somewhat in their effects and hence appear to have rather specific therapeutic values.

Methacholine Chloride, U. S. P. (Mecholyl Chloride)

Acetyl-beta-methylcholine is a choline derivative of sufficient stability in the body to intensify the effects of the parasympathetic system over a period of time. After adequate dosage the heart slows, peripheral blood vessels relax, and the blood pressure falls. There is a general increase in tone in the gastrointestinal tract and an increase in the degree of peristaltic action. Bronchial muscles tend to be constricted, and there is increased activity of the salivary, sweat, and tear glands. The tone of the urinary bladder is increased.

Acetyl-beta-methylcholine may be given orally or subcutaneously, but the intravenous route of administration is considered too dangerous for use. It is to some extent destroyed by gastric juice. Dosage varies with the age of the patient and the effect desired. Symptoms of overdosage usually begin with nausea and vomiting, asthmatic attacks (in susceptible individuals), chest pain (substernal), dyspnea, and fainting. Atropine is considered the best antagonist to use in treatment.

Favorable results have been reported for the use of this drug in the treatment of peripheral vascular disease in which there is spasm and in certain disorders of cardiac rhythm.

Preparations.—

Mecholyl Bromide (Acetyl-beta-methycholine Bromide), N.N.R.

Dosage: 0.2-0.6 Gm. (1-3 tablets) 2 or 3 times daily.

Mecholyl Chloride (Methacholine Chloride), U. S. P. Dosage: 0.2 Gm. (3 gr.) 2 or 3 times daily—orally; 10 mg. ($\frac{1}{6}$ gr.) subcutaneously.

To overcome vascular spasm the oral doses may need to be increased somewhat or the subcutaneous method used.

Carbaminoylcholine Chloride (Doryl)

Carbaminoylcholine is another synthetic derivative of choline which resembles acetyl-beta-methylcholine. It is available in the form of its chloride salt.

It is a strong parasympathomimetic agent. Results of its use suggest that its action is more pronounced on the gastrointestinal and urinary bladder than on the heart. As a result of its action the patient experiences a warmth and flushing in the face, increased flow of saliva, increased peristaltic activity, and increased contractions of the urinary bladder and sometimes of the uterus.

The drug is relatively new and its true therapeutic status has not been fully determined. It has been used in peripheral vascular disease to increase peripheral circulation, promote healing of ulcers, and to relieve pain associated with the vascular condition. It is also used to improve the tone of the urinary bladder and thus prevent urinary retention in patients following surgery, childbirth, etc.

It is given orally and subcutaneously, depending on the effect desired and the patient's ability to tolerate the drug. It produces the same type of toxic effect as acetylcholine. The oral dose varies from 0.2 to 0.8 mg. 2 or 3 times daily. The single subcutaneous dose recommended varies from 0.2 to 0.4 mg.¹

Pilocarpine

Pilocarpine is an alkaloid obtained from the leaves of a South American plant called *Pilocarpus Jaborandi* or *Pilocarpus microphyllus*. The salt most commonly used is **Pilocarpine Nitrate**, U. S. P. The average dose of each drug is 0.005 Gm. ($\frac{1}{12}$ grain). Smaller doses of 0.001 Gm. ($\frac{1}{60}$ grain) are sometimes preferable.

¹Davison, F. R.: *Synopsis of Materia Medica, Toxicology, and Pharmacology*, p. 364.

Action and Uses.—Pilocarpine stimulates the effector cells associated with the parasympathetic nerves. The action is a highly selective one on the reactive substance of cells innervated by post-ganglionic cholinergic fibers.* It thereby increases the secretions of the glands controlled by these nerves, especially the saliva, sweat and mucus from the nose and bronchi. The sweat glands are under control of the sympathetic nerves anatomically, but their response to drugs would indicate that these nerves are parasympathetic. It increases contraction of all the involuntary muscles in the stomach and intestines, bladder, uterus, and bronchi. It contracts the pupil, increases the secretions of tears, and reduces the tension of the eyeball. Internally pilocarpine is used chiefly to produce sweating and thus eliminate waste products through the skin and relieve the kidneys, especially in nephritis. Because of the excessive perspiration, the patient should be wrapped warmly in blankets to prevent chill. In doses somewhat smaller than those required for this purpose, it is of great value in relieving itching in generalized acute eczema, urticaria and pruritus. Locally, pilocarpine is used to lessen pressure within the eyeball in diseases of the eye, such as glaucoma and corneal ulcer.

Poisoning with pilocarpine is not of frequent occurrence, but an overdose may cause weakness, an excessive flow of saliva, tears and sweat, nausea, vomiting and diarrhea, a slow, weak pulse, and rapid, difficult breathing.

Treatment consists in giving atropine ($\frac{1}{60}$ gr.) as an antidote, followed by caffeine or camphor, and artificial respiration. Some poisonous mushrooms when eaten produce symptoms very similar to those of pilocarpine poisoning and the treatment should be the same. Their action is due to an alkaloid called Muscarine.

Physostigmine

History, Source, and Characteristics.—Physostigmine, also known as eserine, is obtained from an African seed known as Calabar bean or "ordeal bean." It was so called because the natives of the Calabar coast of Africa often used it in what is known as "Trial by Ordeal." A person suspected of crime was compelled to swallow some of the powdered bean. If he survived, he was declared innocent; if he died, he was guilty, and there was no escape from the verdict. Physostigmine salicylate occurs as colorless or faintly yellowish, odorless crystals which become reddish on exposure to light and air.

*Goodman and Gillman: *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 389

Pharmacologic Action and Uses.—The action of physostigmine is described as that of sensitization of tissues which are supplied by the parasympathetic nerves. The drug apparently destroys or inhibits the enzyme which ordinarily is responsible for the destruction of acetylcholine. The end result of action is somewhat similar to that of pilocarpine.

When a therapeutic dose of physostigmine is given to man, the main action is upon the eye, the bowel, and skeletal muscle.

1. In the eye, the pupil constricts and the muscle of accommodation goes into spasm. The interocular tension is reduced. The drug may be used to relieve symptoms of glaucoma.

2. The tone and motility of the gastrointestinal tract are increased which explains its use for relief of gastric distention and intestinal paralysis. Some doctors order it for the relief of postoperative gas pains.

3. In normal individuals there is no noticeable effect on skeletal muscle but in patients with myasthenia gravis, improvement may be noted.

Preparations and Dosage.—Physostigmine Salicylate, U. S. P., the official preparation, the average dose of which is 2 mg. ($\frac{1}{30}$ gr.). To restore the pupil to normal after it is dilated, one drop of a 0.1 per cent solution is used. To treat glaucoma and other eye diseases, solutions varying from 0.1 to 1.0 per cent are employed.

Symptoms of Poisoning and Treatment.—The main symptoms of poisoning are pin-point pupils, abdominal cramps, excessive perspiration and flow of saliva, shallow respirations, weak pulse, muscle twitching, and collapse.

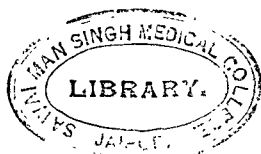
Atropine is the physiologic antidote, but additional drugs in the form of heart stimulants may be required. Keep the patient warm and dry; use artificial respiration as indicated.

Neostigmine, U. S. P. (Prostigmine)

Neostigmine is a synthetic alkaloid belonging to the physostigmine group of drugs. It is available only in the form of its salts, which are freely soluble in water and stable in aqueous solutions.

Action and Uses.—The action of neostigmine is similar to that of physostigmine but has the advantage at being more stable. Compared with the latter it has less effect on circulation and very little effect on the eye. It is as active as physostigmine in stimulating intestinal peristalsis and tone of the urinary musculature. It has been used in the treatment of atonic conditions of the gastrointestinal tract, to





prevent retention in the stomach after gastric surgery, for atonic conditions of the urinary bladder, and in myasthenia gravis.

Myasthenia gravis is a rare and mysterious chronic disease, manifested by extreme fatigability of the muscles. It is most marked in the muscles of the face, but shared to a lesser degree by the other muscles. Ptosis of the eyelids is an almost constant symptom. Nothing is found in the muscles or in the nervous system to account for the myasthenia. One theory of causation, based on the action of physostigmine, is that myasthenia gravis is due to a disturbance or abnormal destruction of acetylcholine at the myoneural junction. The story may be summarized as follows:

1. Acetylcholine is necessary for the transmission of the nerve impulse to the muscle.

2. In case of myasthenia gravis it is destroyed too rapidly by the enzyme, cholinesterase, and the transmission of the nerve impulse is blocked or lessened.

3. Prostigmine or physostigmine acts on the esterase and hinders the destruction of acetylcholine and is of benefit in the disease temporarily.

It should be clearly understood, however, that this is a purely theoretical explanation. There is no good evidence showing that acetylcholine is absent or destroyed too rapidly in myasthenia gravis.

Prostigmine is very effective in removing the symptoms, and is used also in the diagnosis. A dose of 4 to 5 cc. of 1:2000 dilution is given intramuscularly. Improvement of both subjective and objective symptoms of muscular weakness follows almost immediately. When a patient has been elevated to an optimum plane of activity, preparations of prostigmine by mouth may be of value in maintenance.

Myasthenic muscles are high in potassium content, often twice the normal being found. Prostigmine reduces the potassium to within the normal range.

Preparations.—

✓ *Neostigmine Bromide*, U. S. P. (Prostigmine Bromide). Dosage: 15 mg. ($\frac{1}{4}$ grain) orally.

Neostigmine Methylsulfate, U. S. P. (Prostigmine Methylsulfate). Dosage: 0.5 mg. ($\frac{1}{200}$ grain) subcutaneously or intramuscularly.

Neostigmine Methylsulfate Injection, U. S. P. (Prostigmine Methylsulfate Injection). Dosage: 0.5 mg. ($\frac{1}{200}$ grain) subcutaneously or intramuscularly.

DRUGS WHICH INHIBIT THE SKELETAL MUSCLES AND THE AUTONOMIC GANGLIA

Curare

Curare is a poison which is and has been used by South American Indians as an arrow poison. It is obtained from the bark, roots, and stems of several species of plants (*Strychnos*). Curare arrests all connection between the peripheral nerve endings and striated muscles. When large doses are given, one muscle after another becomes weak and flaccid until complete paralysis occurs. Cessation of respiration and heart action follows paralysis of the diaphragm. When administered in carefully regulated doses, it produces great muscular relaxation and has been used to relieve patients with spastic paralysis and to control the convulsive seizures associated with shock therapy. When combined with metrazol, the danger of fractures of the extremities and vertebrae is tremendously reduced. The drug may be taken orally with little or no harmful effect. It may be destroyed in the digestive tract or excreted before much can be absorbed. The therapeutic uses of curare have not been well established, but it is now used by some in anesthesia.

Nicotine

Nicotine is one of the few liquid alkaloids that is readily soluble in water. Large amounts are found in tobacco. It has no therapeutic uses, but its high toxicity and presence in tobacco give it both pharmacologic and medical significance.

Action.—1. Nicotine first stimulates and then depresses the autonomic ganglia, blocking nerve conduction when applied directly to the nerve.

2 Stimulation of the central nervous system, especially the vasomotor, respiratory, and vomiting centers of the medulla, is followed by depression of these centers. Stimulation of the motor areas may cause convulsions. Death is due to the depression of the respiratory center.

Various studies appear to indicate that smoking of tobacco is essentially one method of administering nicotine. Much the same effects can be observed after the intravenous injection of nicotine as occur after cigaret smoking. Nicotine produces an elevation of blood pressure and pulse rate and vasoconstriction of blood vessels. It is therefore contraindicated in patients with coronary artery disease, peripheral vascular disease, and hypertension.

Absorption and Excretion.—Nicotine is readily absorbed from the gastrointestinal tract and respiratory mucous membrane, and from

the skin to some extent. The drug is excreted more slowly than it is absorbed. Tolerance develops when it is repeatedly administered.

Acute Poisoning.—Nicotine is a rapid-acting, extremely toxic drug. Cases have been reported of gardeners who become poisoned while handling the drug in an insecticide preparation. The symptoms are nausea and vomiting, abdominal cramps, diarrhea, faintness, prostration, first a slow and then a rapid pulse, and respiratory failure. Death may occur in a few minutes.

Treatment centers around keeping the patient breathing. Artificial respiration is more effective than central respiratory stimulants. If life can be prolonged enough to give the body a chance to detoxify the drug, the patient may have some chance. Other treatment must be purely symptomatic.

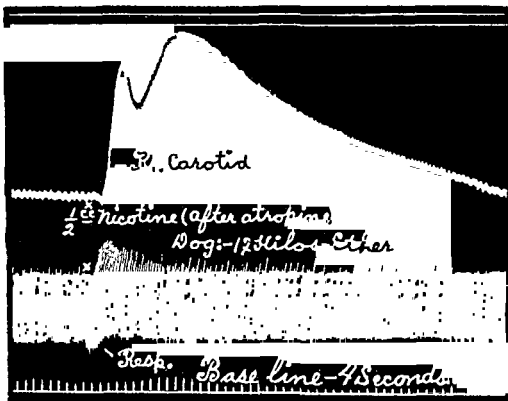


Fig. 16.—Blood pressure and respiratory tracings showing the action of nicotine on the blood pressure after atropine had been given to stop the cardiac inhibition by the vagus. (From Jackson: *Experimental Pharmacology and Materia Medica*)

Suggestions for Study

1. In review of the anatomy and physiology of the autonomic nervous system list the body changes which might be expected when—
 - a. the sympathetic division is stimulated.
 - b. the parasympathetic branch is stimulated.

What effect would the inhibition of one division have over the activity of the other?

2. List the drugs mentioned in this chapter the primary effect of which is on the sympathetic division. Do the same for those which affect the parasympathetic division.
3. Which of the mentioned drugs have been ordered on your ward during the past month? For what purpose were they given? Were the expected results obtained?
4. Which one of the drugs mentioned in this chapter is normally found in our blood and tissue fluids and is greatly responsible for the body changes which occur when we are angered or afraid? Does the hypodermic injection of this drug produce identical effects?
5. Discuss: To what extent is our knowledge of drugs and how they affect body structures dependent upon animal experimentation? To what extent is the resulting knowledge applicable in human beings? How can the nurse develop an appreciation of the methods and technics of science as they are related to a study of drugs?

Questions

1. What are adrenergic and cholinergic drugs?
2. What are the chief alkaloids of belladonna?
3. Describe the action and result of action of atropine.
4. What are the early toxic symptoms of atropine? What can you do about them?
5. How does the central action of atropine and that of scopolamine differ?
6. Explain why scopolamine may be ordered in preference to atropine following brain surgery.
7. Why is homatropine sometimes preferred to atropine for eye examinations?
8. Explain the use of physostigmine or prostigmine for postoperative patients (gastrointestinal surgery).
9. Compare the action of ephedrine and that of epinephrine.
10. Name several drugs which are constituents of nasal sprays. What precautions should be exercised in their use?
11. Name the principal local anesthetics.
12. What is the chief danger involved in the use of cocaine?
13. Compare and contrast cocaine and novocaine.
14. List the local anesthetics which are given in your hospital.

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UNIT IV

CHAPTER XIII

PHARMACOLOGY AS RELATED TO THE DIGESTIVE SYSTEM

Drugs affecting the digestive tract exert their main action on the muscle and gland tissue found in the organs composing the digestive system. The action may be directly on the smooth muscle and gland cells or indirectly on the autonomic nervous system. The student will recall that both divisions of the autonomic system discharge nerve impulses into the tissues of the digestive tube more or less constantly, and under normal conditions maintain a delicate balance of control of functions. Disorders of function result from a variety of causes and treatment likewise varies with the cause of the disorder.

Drugs may bring about increased or decreased function of involved structures, e.g., increased or decreased tone, emptying time, peristaltic action of the stomach or bowel. In addition, they may be given to supply enzyme deficiency, to counteract excess acidity or gas formation, or to kill parasites within the digestive tube.

A. DRUGS AFFECTING THE MOUTH

On the whole drugs have little effect upon the mouth. Good oral hygiene which includes adequate measures of mechanically cleansing the mouth and teeth has more influence than most medicines.

1. **Flavoring Agents** are of use in so far as they make medicines easier to take and thus may have some beneficial effect upon digestive function. Much credit should be given to the pharmacist who skillfully disguises an unpleasant tasting medicine and thus renders it more pleasant to take. Two important preparations used as flavoring agents are glycyrrhiza (licorice) and saccharin. The latter is 300 to 500 times as sweet as cane sugar but is not a food and is readily excreted in the urine. Many syrups, volatile oils, and highly flavored substances are also used.

Flavors attributed to taste may be due to stimulation of smell since smell and taste are so closely associated. Congestion of the nasal mucous membranes may so interfere with the normal sense of

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Flavors attributed to taste may be due to stimulation of smell since smell and taste are so closely associated. Congestion of the nasal mucous membranes may so interfere with the normal sense of

smell that patients will complain of a disagreeable lack of palatability of their food, or that they have a deranged sense of taste. The fact that the sense of taste seems to come back when the nasal congestion is relieved shows that much of our supposed sense of taste is really smell. A coated tongue or cellular debris in a mouth may also interfere with the stimulation of taste buds and may be the reason why patients often complain about institutional food. Adequate oral hygiene will do much to promote a normal sense of taste for the patient.

2. Bitters (< AS. *biter*, to bite).—Bitters are substances with a bitter taste given to improve the appetite. When the appetite is below normal, stimulation of the taste buds with bitters may help restore it. Their effect on appetite is attributed to a reflex stimulation of gastric glands because of the bitter taste. Bitters are prescribed much less frequently today than formerly. Their use in the treatment of poor appetite has been supplanted to a great extent by certain vitamin preparations. Bitters should be administered shortly before meals. Since they are given for their bitter taste, they should be given in solution, mixed with water.

Important Preparations.—

Compound Tincture of Gentian (Tinctura Gentianae Composita), U. S. P. One hundred cubic centimeters represent 10 Gm. of gentian, with bitter orange peel and cardamom seed. Dose: 4 cc.

Compound Tincture of Cinchona (Tinctura Cinchonae Composita), N. F. One hundred cubic centimeters contain 10 Gm. cinchona with bitter orange peel and serpentaria. Dose: 4 cc.

Elixir of Iron, Quinine, and Strychnine (Elixir Ferri, Quininae et Strychninae), N. F. Dose: 4 cc.

3. Mouthwashes and Gargles.—The efficiency of a mouthwash or gargle depends largely on the length of time it is allowed to remain in contact with the affected tissues. Ordinarily they cannot be used strong enough or long enough (particularly gargles) to exert much antiseptic action. A 1 per cent solution of sodium bicarbonate ($\frac{1}{2}$ teaspoonful in a glass of water) is useful to remove mucus from the mouth and throat. A 0.9 per cent sodium chloride solution is probably as good a gargle as most things used.

Sodium perborate is a white, odorless salty-tasting powder which contains not less than 9 per cent available oxygen. It is used in 2 per cent solution as a mouthwash and local disinfectant. Its action results from the liberation of oxygen. It may be obtained in flavored preparations which disguise the salty taste. It is a popular ingredient

of tooth powder and is said to be particularly effective against Vincent's infection and for pyorrhea gum infections. *Potassium Permanganate* 0.1-1 per cent, *Potassium Chlorate* (1 per cent) or *Hydrogen Peroxide* (1:4) may also be used. They are oxidizing agents.

Other substances used in the treatment of stomatitis include thymol, tincture of myrrh, boric acid, formalin, and gentian violet.

Most hospitals have their own favorite mouthwash which may be issued from the pharmacy. The nurse needs to learn the customs of the hospital in this respect as well as others.

4. **Dentifrices, Tooth Powders, or Abrasives.**—Tooth powders are finely divided nonabrasive powders, such as calcium carbonate, magnesium oxide or hydroxide, or sodium perborate. The N. F. contains *Dentifricium* which is mainly flavored, precipitated calcium carbonate containing a little hard soap. Soap per se, while not so tasteful, is perhaps just as good.

The most used dentifrices, abrasives and cleaners are the following preparations, alone or mixed in various proportions:

N. F. Dentifrice	Soap
Precipitated Calcium Carbonate	Sodium Borate
Pumice (flour)	Milk of Magnesia

The essential requirement of a tooth powder or cleaner is that it must not injure the teeth or surrounding tissues. Probably the most that a dentifrice can do is to clean the teeth mechanically.

B. DRUGS AFFECTING THE STOMACH

Drugs affecting the stomach include (1) antacids, (2) digestants, (3) carminatives, (4) emetics, (5) antemetics, (6) drugs used for diagnostic purposes.

1. Antacids .

Hyperacidity should mean a secretion of acid higher than normal. It has been shown, however, that there is no hyperacidity in the sense that the glands produce an abnormally high concentration of hydrochloric acid. The concentration of normal secretion may be just as high as in clinical cases called *hyperacidity*. Instead of *hyperacidity* the term *hypersecretion* has been suggested.* Gastric juice, as it flows from the glands, has a constant acidity.

In practical medicine the term *hyperacidity* refers to gastric distress at various intervals after meals or after the ingestion of special

*Hollander, F., and Cowgill, G. R.: J. Biol. Chem. 91: 151, 1931; 97: 585, 1932; 104: 33, 1934.

kinds of food. Tests with the stomach tube reveal hypersecretion of hydrochloric acid. Hypersecretion is interpreted as being due to (1) increased rate of secretion of normal juice, (2) delayed gastric evacuation, (3) variations in the secretion of neutralizing mucus, (4) failure of normal duodenal regurgitation.

Gastric antacids are drugs which lower the acidity of the gastric content. They are widely used by the laity for a variety of supposed stomach ailments, and by the physician largely for the neutralization of excessive stomach secretion which is associated with some pathologic conditions of the stomach.

They may be classified as systemic and nonsystemic antacids. A systemic antacid is one that is soluble in gastric and intestinal secretions and may be absorbed; it is therefore capable of altering the pH of the blood. The nonsystemic antacids form relatively insoluble compounds which are not readily absorbed and hence are not likely to produce alkalosis. The compounds reduce gastric acidity by physical adsorption or by chemical reactions.

SYSTEMIC ANTACID

Sodium Bicarbonate, U. S. P.—Sodium bicarbonate is used to neutralize the acid of the gastric juice in conditions of hyperacidity and to combat acidosis in conditions of disturbed blood chemistry. It is readily soluble and easily absorbed and therefore constitutes a good example of a systemic antacid.

Although it has a number of therapeutic uses, it has been greatly overused by the laity. It is easily accessible and far too many people feel justified in using it for any number of ailments. People have a fear of an "acid stomach" and fail to recognize that gastric digestion is dependent upon a certain amount of acid being present in the gastric secretion. •

It should be remembered that when the amount ingested exceeds that which is needed to neutralize the acid in the stomach at the time of administration, the excess rather readily passes into the intestine from which it is absorbed and contributes to a disturbance in the acid-base balance in the blood. Likewise, a too frequent use of sodium bicarbonate, even when used in small quantities, may seriously interfere with acid-base balance because of more or less constant neutralization of the gastric acids. Furthermore, gastric digestion of protein is likely to be inhibited because pepsin works best in an acid medium. The latter is less serious since protein is also digested in the intestine.

The reaction of sodium bicarbonate and hydrochloric acid results in the liberation of carbon dioxide. The resulting gastric distention may be quite undesirable, especially if an ulcer is present and near to perforation.

The average dose as an antacid is 1 gram (15 gr.) three times a day.

NONSYSTEMIC ANTACIDS

1. **Precipitated Calcium Carbonate** (chalk), U. S. P., is a fine white powder which is practically insoluble in water but dissolves to a considerable extent in water containing carbon dioxide. It is decomposed by acids, forming a salt of calcium and giving off carbon dioxide with effervescence.

Action and Uses.—Calcium carbonate neutralizes the acid of the gastric juice, and forms with it the soluble calcium chloride. The calcium chloride may again react with sodium bicarbonate in the intestine, with the formation of calcium carbonate which now resists absorption. It is used chiefly as an antacid and protective in hyperacidity, gastritis and gastric ulcer. It has a tendency to constipate and for that reason is especially beneficial in cases in which there is hyperacidity accompanied by diarrhea and in diarrhea with acid fermentation.

Calcium carbonate is given in doses of 1 Gm. (15 grains) in the form of the **Compound Chalk Powder**.

2. **Limewater or the Solution of Calcium Hydroxide**, U. S. P., is a saturated aqueous solution of calcium hydroxide. It is a clear, colorless, odorless liquid having an alkaline, bitter taste.

Limewater is antacid and astringent and is commonly used as an addition to milk to make it more digestible and to lessen curdling. The usual proportion is 1 of limewater to 4 of milk but a mixture of equal parts may be given. This is administered in doses of 15 cc. (4 fl. dr.) to allay nausea, vomiting, and diarrhea. Limewater is used externally in the treatment of burns.

3. **Tribasic Calcium Phosphate** (*Calcii Phosphas Tribasicus*), N. F., has been proposed as an antacid. It is given to neutralize excess of acid in the stomach. It has the advantage over sodium bicarbonate and magnesium hydroxide in being less soluble, and less likely to produce alkalosis. Dibasic, U. S. P., is preferable.

Dose.—From 1 to 5 Gm. (15 to 75 gr.).

4. **Magnesium Carbonate**, U. S. P., is a bulky white odorless powder with a slightly earthy taste. It is practically insoluble in water but soluble with effervescence in dilute acids, with which it forms salts of magnesium.

Magnesium carbonate when taken internally neutralizes the acid in the stomach and is used for this purpose in cases of hyperacidity or acid gastritis. It is sometimes objectionable, however, because of the carbon dioxide gas evolved.

5. **Magnesium Oxide, U. S. P. (Light Magnesia)**, is a bulky white odorless powder with an earthy taste. It is almost insoluble in water but dissolves readily in acids, forming salts of magnesium which are laxative. Magnesium oxide is used chiefly as an antacid to neutralize excessive acidity in gastric juice, and is especially indicated in cases of hyperacidity accompanied by constipation. It is preferable in most cases to the carbonates or bicarbonate because it yields no gas on being neutralized. Magnesium oxide is sometimes given in diarrhea with excessive acidity in children.

As an antacid the average dose is 0.25 Gm. (4 gr.); as a laxative, 4 Gm. (60 grains).

Magnesia Magma (Magma Magnesiae), U. S. P. (Milk of Magnesia, Magnesia Hydroxide). Dose: Antacid—4 cc.

6. **Magnesium Trisilicate, U. S. P.**, is a white odorless, tasteless powder insoluble in water but slightly or partially soluble in acids. It is said to compare favorably with other antacids of the nonsystemic variety. In the stomach it assumes a gelatinous consistency and acts as an effective adsorbent as well as a chemical antacid. The single dose is 1 to 4 drams.

7. **Aluminum Hydroxide Gel, U. S. P.** for medicinal purposes is prepared in a colloid suspension in which its action is more physical than chemical. It is said to act in the following ways: (1) as a chemical antacid, (2) as an adsorbent of gases, toxins, and hydrochloric acid, (3) as a protective for irritated gastric membrane, (4) as an astringent glue to the formation of small amounts of aluminum chloride.

Excessive amounts of aluminum hydroxide may interfere with the absorption of certain minerals and may cause phosphorus deficiency.*

Aluminum Hydroxide is marketed under a variety of trade names in both powder and liquid forms.† It is administered orally in one-half glass of water or milk every two to four hours, or one-half to one hour after meals; dose, 0.6-1 Gm. (5-10 cc.).

Aluminum Phosphate Gel, U. S. P. The properties of Aluminum Phosphate are similar to those of Aluminum Hydroxide, but do not interfere with phosphate absorption. Dosage: 8 cc. alone or in milk or water.

*N. N. R., 1947, p. 316.

†Goodman and Gilman. The Pharmacological Basis of Therapeutics, The Macmillan Co., p. 787

2. Digestants

Digestants are drugs which promote the process of digestion in the gastrointestinal tract and constitute a type of replacement therapy in deficiency states.

Hypochlorhydria, Achlorhydria.—These terms denote a decreased secretion of hydrochloric acid in the stomach. It may occur when the pepsin and rennin are normal or diminished in amount. When ferments and acids are both absent the condition is called *achylia gastrica*.

A deficiency of acid in the stomach may be due (a) to deficient secretion, or (b) to excessive secretion of mucus which neutralizes the secretion, or (c) to regurgitation of alkaline substances from the intestine.

Achlorhydria is common in carcinoma of the stomach. It is rather regularly associated with pernicious anemia; it occurs in various infectious diseases and may occur in renal disease, gout, and diabetes. It may be found in some apparently normal individuals.

Causes may be manifold, but are not well understood. In pernicious anemia the condition may appear before the blood changes. Some forms may be due to defective vagal innervation. It may also be due to the lack of some hormone. The treatment indicated is to supply the missing elements. The use of predigested foods and of hydrochloric acid and pepsin may be of assistance.

Diluted Hydrochloric Acid, U. S. P., contains 10 per cent hydrochloric acid. This needs to be diluted with 25 to 50 volumes of water and should be taken with a glass tube to avoid injury to the teeth. The average dose is 4 cc. diluted with water, during or just after meals.

Malt (Maltum), extract of malt, is prepared from germinated barley. It is a sweet, light-brown liquid extract, and contains dextrin, maltose, glucose, and amylolytic enzymes. It is used to aid carbohydrate digestion. Dose: 15 Gm. (4 dr.).

Pancreatin (Pancreatinum) is a cream-colored amorphous powder, prepared from the pancreas of the hog or ox, and contains amylopsin, trypsin, and steapsin. Dose: 0.5 Gm. (8 gr.).

Pepsin (Pepsinum) is prepared from the glandular layer of the fresh stomach of the hog. It is available in the form of transparent or translucent scales. It is used to aid protein digestion, mainly in the stomach. Dose: 0.5 Gm. (8 gr.).

Bile and Bile Salts.—Bile is composed chiefly of water, bile salts, cholesterol, and lecithin. It is essential for normal digestion of fats, for absorption of fatty acids, carotene, vitamins A, D, and K, and it also promotes normal peristaltic activity in the intestine. Bile

salts are combinations of bile acids and amino acids. They are secreted by the liver and reabsorbed in the intestine. Patients with derangement of the liver or bile ducts are prone to have nutritional and digestive disturbances. Bile or bile salts may be administered for their relief. They do not increase bile secretion.

Preparations.—

Extract of Ox Bile, U. S. P., a dry powder made from the fresh bile of the ox. Average dose 0.3 Gm.

Glycotauro. Concentrated ox bile freed from bile pigments, containing more than 50 per cent of the natural mixture of sodium glycocholate and sodium taurocholate. Each gram represents approximately 15 cc. of fresh ox bile.

Decholin (Dehydrocholic Acid), N. N. R. An oxidation product of cholic acid derived from natural bile acids. It is useful to increase the volume of bile and to increase drainage of bile ducts. Dosage 0.25 to 0.5 Gm. (4-8 grains) two or three times daily.

Decholin Sodium (Sodium Dehydrocholate), N. N. R. A form which can be given intravenously on each of three successive days, using 5 to 10 cc. of a 10 or 20 per cent solution.

3. Carminatives

Carminatives are drugs that aid in the expulsion of gas from the stomach or intestine.

In intestinal diseases, gas is formed in abnormal quantities, and those that are least rapidly absorbed are produced in greatest abundance.

In the normal intestine, the gases are either absorbed or expelled, but in pathologic conditions tympanites may develop. Inflammatory conditions, such as peritonitis and acute strangulation, lessen the absorptive rate and the intestines yield to the pressure within them, so creating a vicious circle by diminishing the circulation which in turn diminishes absorption, and so flatulence develops.

It has generally been assumed that carminatives favor the escape of gas by relaxing the gastric and intestinal musculature. Plant favors the view that they act by stimulating intestinal rhythmic contractions and thus increasing muscular activity. In cases of peritonitis and other inflammatory diseases carminatives, by increasing movement, may spread the infection and should not be used, or used with care. In cases of paresis of the gastrointestinal musculature following surgical operations or severe infections, such as typhoid fever or pneumonia, the carminative oils are less valuable than the more powerful smooth muscle stimulants—physostigmine or pituitrin.

With the exception of alcohol, ammonia, ether, and chloroform, carminatives are aromatic bodies, containing volatile oils as the active ingredient. The most important carminatives are:

Anise	Cinnamon	Nutmeg
Asafetida	Cloves	Oil of turpentine
Cajuput	Compound spirit	Pepper
Capsicum	of ether	Peppermint
Caraway	Coriander	Pimenta
Cardamom	Ether	Sassafras
Chloroform	Fennel	Spearmint
	Ginger	

From their therapeutic uses, Bastedo classifies carminatives as follows:

1. As anticolics (in intestinal and uterine cramps). Especially employed for infants are anise, peppermint, and dill water, and for adults the distilled liquors, essence of ginger, spirit of peppermint, aromatic spirit of ammonia, and Hoffmann's anodyne (the compound spirit of ether).

2. As odors and flavors—*anise*, bitter almond, *caraway*, *cinnamon*, *coriander*, *fennel*, lavender flowers, *lemon*, *nutmeg*, orange-peel, *peppermint*, *spearmint*, *rose*, and *vanilla*. Of the waters, the dose is 1 fluidram (4 cc.); of the spirits, 5 minims (0.3 cc.).

3. As correctives of irritant cathartics—the oils of *anise*, *caraway*, *cloves*, *coriander*, *fennel*, and *peppermint*. Of the oil, $\frac{1}{4}$ minim (0.015 cc.); or of the drug, 1 grain (0.06 Gm.), to each dose.

4. For tympanites, as in typhoid fever, pneumonia, or following operations. By mouth, oil of turpentine, 10 minims (0.07 cc.) in capsule; or *asafetida*, 5 grains (0.03 Gm.) in pill or tincture. By rectum, oil of turpentine, $\frac{1}{2}$ ounce (15 cc.); or tincture of *asafetida*, 1 fluidram (4 cc.), added to a soapsuds enema or to 8 ounces or more of infusion of chamomile (an aromatic bitter).

4. Emetics

Emetics are drugs which produce vomiting and may be divided into two classes:

1. Those that act peripherally, or that attack the center reflexly.

The *reflex emetics* act by irritating the throat or stomach. Emesis may be caused by tickling the throat with a feather, or with the finger, or by the use of one of the following:

Mustard, U. S. P., a teaspoonful to a tablespoonful given in tepid water, repeated every 15 minutes if necessary.

Warm water. Lukewarm water given repeatedly will produce vomiting.

Warm soap suds.

Sodium chloride in concentrated solutions will cause vomiting.

Alum, 1-2 Gm. (15-30 gr.), in solution.

Copper sulfate, 1-2 Gm. (15-30 gr.), in solution.

Antimony and potassium tartrate (tartar emetic), 0.03-0.12 Gm. ($\frac{1}{2}$ 2 gr.).

Zinc sulfate, 0.6-1 Gm. (10-15 gr.).

Fluidextract of Ipecacuanha, 1 cc. (15 min.). Ipecac is more important as an amebicide and as an expectorant.

All peripheral emetics are irritant and may do serious damage to the stomach if vomiting fails; hence the dose should not be given more than twice. They should be given in solution when dry drugs are used.

2. Central emetics act directly on the vomiting center. The only central emetic in common use is apomorphine hydrochloride. The emetic dose is 0.005 Gm. ($\frac{1}{12}$ grain), given hypodermically. Vomiting is usually elicited in a very few minutes. Large doses produce a central depression; therefore the drug should not be given to a patient who is depressed. It is used mainly to induce vomiting in cases of poisoning. As is true of most emetic drugs, apomorphine in smaller doses acts as an expectorant.

5. Antemetics

Antemetics are drugs used to check nausea and vomiting. The control of vomiting is an important and often difficult problem. Numerous drugs have been used and the treatment depends on the cause. Vomiting may be due to central or reflex action. The latter is by far the most common.

Drugs Most Used.—Sodium bicarbonate is used to neutralize acidity and as a local sedative; bismuth subcarbonate and bismuth subnitrate are used as protectives, and calcium carbonate and magnesium hydrate are employed for the same reason. Cathartics and enemas are used where there is constipation. Carbonated drinks are popularly used to relieve nausea when there is gaseous distention or hyperacidity.

Local anesthetics, such as cocaine, apothesine, anesthesin, are given with the object of allaying pain developing from a lesion. Lavage may be used to remove it. Bromides and cerebral depressants may be given to depress the vomiting center. When vomiting has dehydrated the body, dextrose solutions intravenously in 25 per cent solution have proved valuable. The reason for the use of all these may be found in the discussion of these drugs.

6. Drugs Used as Test Agents or for Diagnostic Purposes

Histamine Phosphate, U. S. P. Histamine acts strongly on the gastric glands (as on most glands), causing an increase in the secretion of water, hydrochloric acid and inorganic constituents, without affecting the secretion of enzymes



Fig. 17.—Gastric carcinoma (cancer) as revealed by an x-ray photograph. The stomach has failed to fill uniformly with barium sulfate, due to the presence of the carcinoma (see arrows). What change in the hydrochloric acid content of gastric juice usually accompanies cancer of the stomach? (From Meakins: *The Practice of Medicine*, The C. V. Mosby Co)

Histamine is used as a diagnostic agent in cases of suspected achylia gastrica, e.g., in the course of pernicious anemia. It has little action when given by mouth and is given intramuscularly. In normal individuals 0.5 mg. of histamine (0.85 mg. of the phosphate) intramuscularly gives the maximal secretion of acid in from one-half to one hour. In achylia vera the acid response is absent. The injection may produce marked side reactions, such as a wheal at the

site of injection (more marked if given subcutaneously), headache, vertigo, and flushed face.

Alcohol.—Instead of a test meal, 7 per cent alcohol is sometimes used. It will show whether or not the stomach is capable of secreting acid. It directly stimulates the gastric glands.

Barium Sulfate (*Barii Sulfas*), U. S. P., is a fine, white odorless, tasteless, and bulky powder, free from grittiness. It is insoluble in water, in organic solvents, and in aqueous solutions of acids and alkalies. This property of insolubility explains the safety which accompanies its use, for all soluble barium salts are exceedingly poisonous. It is much more impermeable to x-rays than is tissue,



Fig. 18.—X-ray photograph showing carcinoma (cancer) of the rectum. Notice that the cancer prevents complete filling of the rectum by this barium sulfate (see arrows). The barium sulfate was given in the form of an enema. How might examination of the feces help in diagnosing this condition? (From Meakins: *The Practice of Medicine*)

and for that reason is used in x-ray photography of the gastrointestinal tract. The patient is usually examined first by means of the fluoroscope and flat plates are later taken at intervals to determine the rate of passage of the barium through the digestive tract and to locate areas of abnormality. The patient is usually given a cleansing enema following the test.

PHARMACOLOGY AS RELATED TO THE INTESTINE

Drugs acting on the bowel are here grouped under *cathartics*, *antidiarrheics*, and *anthelmintics*.

CATHARTICS

Hygiene of Elimination.—The principles of hygiene of elimination are taught in other courses and should not need special emphasis here, except for the fact that nurses see so many cathartic preparations ordered for hospital patients they are likely to arrive at a mistaken conclusion as to the conditions under which the use of cathartics is suitable or advisable. They rather easily develop a disregard for the dangers associated with overuse, and fail to understand that sick people, who are unable to move about freely or are under the influence of drugs which inhibit peristaltic activity or patients whose diets are greatly restricted, present a need for cathartics far different from that of the so-called normal individual.

People in general harbor a popular misconception about the function of the colon. They regard it solely as a sewer of the body which requires frequent cleansing, rather than a portion of the alimentary tube closely allied to the rest of the digestive system. The colon provides a place where fluid is absorbed and when the remaining residue accumulates to the extent that the colon is slightly overdistended, peristalsis is stimulated and the content forced into the lowest portion of the bowel. The colon is never normally empty, hence "cleaning" of this organ is rarely necessary in the normal person.

When the fecal content remains in the colon longer than usual, water continues to be absorbed and the content gradually becomes hardened, thus resulting in constipation. This condition is then primarily a matter of stool consistency rather than amount or frequency. The frequency of bowel movement depends greatly on the individual. If an individual has a bowel movement once a week but the stool passed at that time is of normal consistency and the person is comfortable after the passage, the frequency of elimination should be considered quite normal for that individual in spite of the fact that the bowels of most persons empty more often.

Causes of Constipation.—These may be general or local. The *general causes* are: (1) Improper diet—one that leaves too little residue. Diets may also be lacking in vitamins. (2) Constitutional peculiarities, such as muscular weakness of the colon. (3) Sedentary habits. (4) Certain diseases, such as anemia, neurasthenia, hysteria, affections of the liver, stomach, or intestines, and acute fevers. (5) Drug habits, such as morphine addiction. (6) Neglect to respond to normal defecation impulses, etc.

Local Causes.—(1) Weakness or atony of the abdominal muscles in obesity or resulting from pregnancy or tumors. (2) Disease of the intestines and mucosa. (3) Tumors pressing on the bowel. (4) Anal fissure.

Whatever the exciting cause of constipation, it results finally because there is too little fluid in the intestine, due to too great absorption. Water is a cathartic if it is held in the intestine.

Furthermore, constipation should be looked upon as a symptom of a number of disease conditions rather than a disease in itself. Many persons find relief when more attention is paid to simple hygienic rules, i.e., adequate exercise, food, fluids, prompt response to the call for defecation, and freedom from worry. If these measures do not afford the desired relief, it is important that a physician be consulted since a physical examination may uncover a serious disease condition which demands prompt attention and treatment. Symptoms associated with constipation and often attributed to self-intoxication are debility, lassitude, vertigo, mental depression, headache, loss of appetite, coated tongue, etc. There is evidence, however, that these symptoms are the result of distention of the lower bowel and not to the absorption of toxic products.

RESPONSIBILITIES OF THE NURSE IN RELATION TO THE USE OF CATHARTICS

The nurse must exercise great caution in the giving of "cathartic advice." Persons who seek help because they have become increasingly dependent upon cathartics need the advice of a physician and should be persuaded to go to one. Not only should the cause of the constipation be found and corrected, but the patient should be broken of his psychic dependence upon the medication. Another reason why a nurse should exercise discretion when consulted about the use of cathartics is that people are prone to take a cathartic to relieve abdominal pain, nausea, or general gastrointestinal discomfort. An inflamed appendix may be ruptured by increased peristaltic activity, and the mortality rate of this disease thus adversely affected.

She should rather direct her efforts to the teaching of basic facts concerned with the hygiene of elimination so as to prevent constipation; the eating of an adequate diet, taking regular exercise, drinking plenty of fluids, and the development of regular habits of defecation. She may be able to help some patients by persuading them to eat all the food that is served to them, by providing plenty of drinking water and encouraging the patient to drink it, and by providing for as much exercise as the patient is allowed.

Contraindications for Cathartics.—

There are a number of conditions in which cathartics are contraindicated or must be given with caution, including the following:

1. Inflammatory conditions along the alimentary tract—appendicitis, typhoid fever, etc.
2. Conditions of undiagnosed abdominal pain.
3. Chronic constipation.
4. Following surgery of the bowel, stomach, or rectum.
5. Pregnancy, anemia, or in states of marked debilitation.

Indications for Cathartics.—

1. In most cases of food or drug poisoning or gastrointestinal upsets of childhood.
2. To check certain types of diarrhea, by removing the irritating material.
3. To relieve edematous conditions of the body including increased intracranial pressure (saline cathartics).
4. Certain cases of acute constipation.
5. To keep the stool very soft when it is essential to avoid the irritation which accompanies the passage of a hardened stool, e.g., patients with a colostomy, rectal conditions or irritated polyps in the bowel or when straining is to be avoided, as after hernia repair or cerebral accident. The type of cathartic used in these conditions would of course be limited to something like liquid petrolatum.
6. Certain cathartics are sometimes used to initiate labor.

Classification of Cathartics.—Cathartics may be classified according to their source, site of action, degree of action, and method of action. The latter two classifications will be described.

A. According to degree of cathartic action.

1. *Laxatives*—cathartics which cause few movements of the bowel; the stool is formed and normal in appearance and unaccompanied by griping.
2. *Purgatives*—cathartics which produce frequent movements with soft or liquid stools which may or may not be accompanied by griping.
3. *Drastics*—cathartics which produce frequent watery stools accompanied by severe griping.

The above classification is not a hard and fast one because dosage is frequently the determining factor. A small dose of some cathartics may have a laxative effect while a larger dose may cause a purgative effect.

B. According to method of action.

1. Cathartics may stimulate peristalsis by increasing the fluid, gaseous, or solid bulk of the intestinal content.
2. By chemical irritation of the intestinal tract thus producing greater motor activity.
3. By a selective action on the neuromuscular mechanism of the intestine, after absorption. These preparations are usually given hypodermically and are used to relieve distention and intestinal ileus more than to promote elimination of the solid waste material.

Cathartics Which Act by Increasing Bulk

Constipation may result from eating too little food or from eating too concentrated food which leaves little residue in the intestinal tract. Under such conditions, the use of bulk-forming cathartics or those which serve to lubricate the passage of fecal material may be helpful.

Liquid Petrolatum (*Petrolatum Liquidum*), U. S. P. Liquid Paraffin or Mineral Oil is a mixture of liquid hydrocarbons obtained from petroleum. The oil is neither digested nor absorbed. It lubricates the fecal mass and prevents excessive absorption of water. It is especially useful when it is desirable to keep feces soft and when straining at stool must be minimized, as after rectal operations, repair of hernias, or after cerebrospinal accidents. Because it acts as a laxative it is useful for patients who have a chronic type of constipation which may be due to prolonged inactivity. Such would be the case in patients with some orthopedic conditions.

Some physicians object to the use of mineral oil on the basis that it dissolves certain of the fat-soluble vitamins and bile salts and thus inhibits their absorption. Others maintain that only the precursor to vitamin A (carotene) is so affected and that natural vitamin A is quantitatively absorbed from the intestine in the presence of mineral oil.* Another objection to its use is that in large doses it tends to seep from the rectum and soil clothing or destroy rubber sheets on hospital beds. The dose is from 15 to 30 cc. and is best given between meals or at bedtime. It should not be given immediately after meals, as it may delay the passage of food from the stomach. Most patients may have a slice of orange just after taking the oil to help cleanse their mouth of the oil. When mineral oil is purchased, it is important to get an oil of the U. S. P. standard.

*Davison, F. R.: *Synopsis of Materia Medica, Toxicology and Pharmacology*.
p 236

Olive oil and cottonseed oil are digestible oils but if given in sufficient quantity may act by increasing bulk since a part of the oil will escape hydrolysis and will act as a lubricant.

Agar, U. S. P., a dried mucilaginous substance obtained from several varieties of seaweed. It may be obtained in the powdered, granular, or flaked form. The granular preparation is the one most desirable as a rule. Agar is rich in indigestible cellulose. When moistened it swells, forming a mass of material which passes through the intestine without being affected by the digestive juices and by its blandness and bulk makes the stool large and soft so that it is easily moved along the colon and into the rectum. It is one of the best bulk-forming cathartics. It is best taken twice daily in doses of $\frac{1}{2}$ to 1 ounce accompanied by plenty of fluid. Some find agar more palatable when it has been allowed to soak in hot water and is then added to such food as cereal, soup, or mashed potatoes or is merely taken in the soft semi-liquid form. When the dry agar is used, it likewise may be added to soup, cereal, potatoes, pudding, etc. It also may be emulsified with liquid petrolatum (Petrogalar). Cascara, phenolphthalein, or milk of magnesia is sometimes added to the emulsified form.

The effect of agar is not noticed immediately. It may require a week or two to establish satisfactory evacuation, but as soon as results seem satisfactory, the dose should gradually be reduced to the smallest amount needed for a satisfactory bowel movement. Doses should then be omitted occasionally until its use is no longer necessary. This gradual reduction and cessation of dosage should constitute a principle underlying the use of all laxative cathartics to avoid undesirable reactions and habit formation.

Plantago Seed (Psyllium Seed), N. F., is also a bulk-forming cathartic. It is a small brown seed which in the presence of water forms a considerable amount of mucilaginous material which absorbs more water, swells and thus forms a larger stool. The main disadvantage lies in the fact that although the seeds swell, their ends remain sharp and may be the source of considerable irritation. Many doctors disapprove of their use for this reason. Psyllium flour is made by grinding the seeds and removing the fiber. In this form it is a constituent of many proprietary preparations along with mineral oil, cascara, etc. There is evidence that the ground psyllium seed may produce damage in the kidney, hence its use is somewhat questionable. Metamucil (Searle) is a preparation of the mucilaginous portion of the seed held in suspension with dextrose. Average dose: $7\frac{1}{2}$ Gm. (2 drams).

Sublimed Sulfur (Sulfur Sublimatum), U. S. P., increases bulk by the formation of intestinal gases in the form of sulfides and sulfates which permeate the fecal content and give rise to soft stools. Much of the sulfur is excreted unchanged. Some of the sulfide is absorbed and excreted in the breath. Sulfur was at one time a popular constituent of the old-fashioned "spring tonic." It is a constituent of compound licorice powder (see Senna).

Other substances which form bulk are preparations of bassorin paste and manna.

Saline Cathartics

Saline cathartics are soluble salts that are relatively nontoxic and nonabsorbable. They are nontoxic because they are not absorbed, but exert toxic actions when injected intravenously. The most important saline cathartics are magnesium citrate, magnesium sulfate, sodium sulfate, sodium phosphate, and sodium potassium tartrate.

What is the mechanism of saline catharsis? No explanation yet offered is satisfactory in every detail. Differences of opinion exist mainly concerning the relative importance of:

1. The prevention of water absorption by saline.
2. The withdrawal of fluid from the blood and tissues to the gut
3. The specific stimulating action of the salt on peristalsis.

The Modern Explanation.—Solutions of cathartic salts remain in the gut and are but slightly absorbed. Why absorption does not take place we do not know, since these salts dialyze readily. Because they are not absorbed, they retain water in the gut and prevent its absorption. The retention of water is explained by osmosis which is developed because the gut acts as a semipermeable membrane for these salts. The volume of water in the gut hastens the passage of the contents to the colon and rectum where defecation reflexes are stimulated. The cathartic ions, because of their slight irritant action, may stimulate some intestinal secretion and peristalsis.

The presence of water in the intestines is a necessity for saline catharsis. It has been demonstrated that a concentrated solution of magnesium sulfate given to thirsting animals causes no purgation while dilute solutions cause rapid purgation. This shows that the retention of water in the gut is probably the most important factor.

Saline cathartics are usually administered as hypertonic or isotonic solutions. They bring about a loss of fluid from the bowel and hence from the general circulation. Repeated administration will cause general tissue dehydration and are therefore to be avoided

in patients who are already dehydrated. The saline cathartics are the cathartics of choice to deplete the body of edema, although they have other uses as purgatives as well.

Absorption.—The intestinal membrane is not entirely impermeable to the passage of the saline cathartics. Some find their way into the general circulation only to be excreted by the kidneys, in which case they may act as saline diuretics, depending on the strength of the solution originally administered. Hypertonic salt solutions may result in so much loss of body fluid by way of the bowel that little or no diuretic action will be possible.

Therapeutic Uses.—Saline cathartics are used (1) for treatment of acute constipation (chronic cases are better treated with other cathartics, especially cascara and laxative foods), (2) for intestinal putrefaction, (3) edematous conditions and those of increased intracranial pressure, (4) to lessen milk secretion, (5) to secure stools for examination, (6) in cases of food poisoning.

When the object is merely to empty the intestine, magnesium citrate, magnesium sulfate, sodium phosphate, or milk of magnesia is effective. Milk of Magnesia (Magnesium Hydroxide) is the mildest of the salines and is best suited for children. Heavy Magnesium Oxide is better for adults as a rule. Magnesium Sulfate is probably the best to relieve edema, although it has a disagreeable taste. Sodium sulfate is the most disagreeable and not much used except in veterinary practice. The effervescent preparations are the most agreeable to take.

Administration.—The salines tend to have a rapid action, especially if taken in the morning before breakfast. Their action is upon the entire intestine and evacuation is secured in from one to four hours. Hypertonic solutions should be given when relief of edema is desired. Patients sometimes complain of gaseous distention after taking salines. All preparations should be accompanied by a liberal intake of water since the salts do not readily leave the stomach unless well diluted. On the other hand, if the saline is given to reduce edema, the patient's total daily intake of fluids will probably be restricted.

Preparations and Dosage.—

Sodium Sulfate (Sodii Sulfas, Glauber's Salt), U. S. P., Dose: 15 Gm. ($\frac{1}{2}$ ounce) orally. Glassy crystals or a white powder, readily soluble in water, and with a strong disagreeable saline taste.

Sublimed Sulfur (*Sulfur Sublimatum*), U. S. P., increases bulk by the formation of intestinal gases in the form of sulfides and sulfates which permeate the fecal content and give rise to soft stools. Much of the sulfur is excreted unchanged. Some of the sulfide is absorbed and excreted in the breath. Sulfur was at one time a popular constituent of the old-fashioned "spring tonic." It is a constituent of compound licorice powder (see *Senna*).

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Saline Cathartics

Saline cathartics are soluble salts that are relatively nontoxic and nonabsorbable. They are nontoxic because they are not absorbed, but exert toxic actions when injected intravenously. The most important saline cathartics are magnesium citrate, magnesium sulfate, sodium sulfate, sodium phosphate, and sodium potassium tartrate.

What is the mechanism of saline catharsis? No explanation yet offered is satisfactory in every detail. Differences of opinion exist mainly concerning the relative importance of:

1. The prevention of water absorption by saline.
2. The withdrawal of fluid from the blood and tissues to the gut
3. The specific stimulating action of the salt on peristalsis.

The Modern Explanation.—Solutions of cathartic salts remain in the gut and are but slightly absorbed. Why absorption does not take place we do not know, since these salts dialyze readily. Because they are not absorbed, they retain water in the gut and prevent its absorption. The retention of water is explained by osmosis which is developed because the gut acts as a semipermeable membrane for these salts. The volume of water in the gut hastens the passage of the contents to the colon and rectum where defecation reflexes are stimulated. The cathartic ions, because of their slight irritant action, may stimulate some intestinal secretion and peristalsis.

The presence of water in the intestines is a necessity for saline catharsis. It has been demonstrated that a concentrated solution of magnesium sulfate given to thirsting animals causes no purgation while dilute solutions cause rapid purgation. This shows that the retention of water in the gut is probably the most important factor.

Saline cathartics are usually administered as hypertonic or isotonic solutions. They bring about a loss of fluid from the bowel and hence from the general circulation. Repeated administration will cause general tissue dehydration and are therefore to be avoided

Sodium sulfate is the basis of many proprietary cathartics such as Pluto Water, Crazy Water Crystals, or Sal Hepatica. Mineral waters are usually artificially prepared solutions made in a factory and contain magnesium sulfate or sodium sulfate or both. Their use in the treatment of constipation is thought inadvisable.

Cathartics Which Act by Irritation

CATHARTIC OILS

1. Castor Oil (*Oleum Ricini*) is obtained from the seeds of the castor bean (*Ricinus communis*), a plant which grows in India but is cultivated in a number of places where the climate is warm. It is a colorless bland emollient which passes through the stomach unchanged but like other fatty substances retards the gastric emptying time. For this reason it is usually given on an empty stomach. In the intestine the oil is hydrolyzed like any fat to glycerin and a fatty acid which in this case is ricinoleic acid. Both the acid and the resulting salts (ricinoleates) formed in the intestine are responsible for the purgative effect. When given by mouth the oil is saponified and the effect of the free acid is obtained immediately. Consequently castor oil is practically "fool proof" and may be given in large doses since as soon as sufficient is hydrolyzed, the resulting cathartic action carries away the superfluous unsaponified oil. Castor oil acts mainly on the small intestine; it rarely reaches the large intestine before acting. The site of action may be observed with a fluoroscope.

A therapeutic dose of castor oil will produce several semifluid stools in from two to six hours after administration. There is little or no intestinal griping associated with this cathartic. The fluid nature of the stool is due to the rapid passage of the fecal content rather than to a diffusion of fluid into the bowel.

In sensitive individuals the natural oil may be unpleasant and nauseating. This may be overcome by the use of fruit juices or pharmaceutical mixtures to disguise the oil. Some care should be exercised, especially in children, to prevent untoward conditioning of the child against such things as orange juice. Each hospital is likely to have its own particular way of administering castor oil and the nurse should learn the recipe of the institution in which she works.

Therapeutic Uses.—Castor oil is especially indicated for:

- a. Food or drug poisoning.
- b. Fermentative diarrhea and dysentery.

Magnesium Sulfate (Magnesii Sulfas, Epsom Salts), U. S. P. Dose: 15 Gm. ($\frac{1}{2}$ ounce) orally. Glassy crystals or white powder, readily soluble in water, with a disagreeable taste.

Milk of Magnesia (Magma Magnesiae), U. S. P. (Magnesium Hydroxide). Dose: As a cathartic 15 cc. (4 drams) orally. Used more commonly as an antacid. In the stomach the magnesium hydroxide reacts with the hydrochloric acid, forming magnesium chloride which then acts as a saline cathartic in the bowel.

Magnesium Oxide (Magnesii Oxidum), U. S. P. Dose: As a cathartic 4 Gm. (60 grains) orally. The cathartic action depends upon the conversion of the oxide in the intestinal tract into soluble salts.

Magnesium Carbonate (Magnesii Carbonas), U. S. P. Dose: As a cathartic 8 Gm. (2 drams) orally. A bulky white powder practically insoluble in water. Used as an antacid as well as a cathartic. Cathartic action is dependent on formation of a soluble salt in the intestinal tract.

Solution of Magnesium Citrate (Liquor Magnesii Citratis), U. S. P. Dose: $\frac{1}{2}$ to 1 bottle (6-12 ounces) orally. Magnesium Citrate is not very soluble hence the need for a relatively large dose. It is pleasant to take because it is carbonated and flavored.

Sodium Phosphate (Sodii Phosphas), U. S. P. Dose: 4 Gm. (1 dram) orally. White crystalline substance readily soluble in water. Taste less disagreeable than that of sodium or magnesium sulfate.

Effervescent Sodium Phosphate (Sodii Phosphas Effervescens), U. S. P. Dose: 10 Gm (2 $\frac{1}{2}$ drams). Made effervescent by the addition of sodium bicarbonate, and citric and tartaric acids.

Potassium Sodium Tartrate (Potassii Sodii Tartras), U. S. P. (Rochelle Salt). Dose: 10 Gm. ($\frac{1}{3}$ ounce) orally. This preparation occurs as crystals or white powder; very soluble, and has a not unpleasant taste.

Compound Effervescent Powders (Pulveres Effervescentes Compositi), U. S. P. (Seidlitz Powders). Dose: The contents of a blue and a white paper dissolved separately in about $\frac{1}{3}$ of a glass of water and the solutions mixed at the bedside or just prior to swallowing. The blue paper contains sodium and potassium tartrate and sodium bicarbonate. The white paper contains tartaric acid. The effervescence is caused by the liberation of carbon dioxide when the sodium bicarbonate and tartaric acid interact. The effervescence does much to increase the palatability of the mixture.

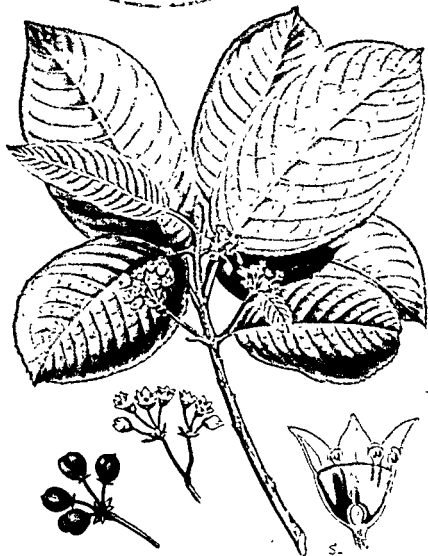


PLATE X—*Rhamnus purshiana* (Buckthorn) (From Jackson: *Experimental Pharmacology and Materia Medica*)

- c. For the initiation of labor in obstetrics.
- d. For preoperative preparation of the bowel or for cleansing of the bowel prior to x-ray.
- e. In marked constipation, although it is counterindicated in chronic constipation.

Preparations.—

Castor Oil (*Oleum Ricini*), U. S. P. Dose: 15 cc. (4 fl. dr.). It has an unpleasant taste when given alone, and is best given in an emulsion flavored with some volatile oil, or in orange juice, spirits, or glycerin, or in flexible capsules.

Oleum Ricini Aromaticum, N. F., is a rather pleasant flavored preparation. Dose: 15 cc. (½ oz.).

2. *Croton Oil* (*Oleum Tiglii*) is a fixed oil obtained from the seeds of *Croton tiglium*.

Unlike castor oil, croton oil must be handled with caution, as it causes pustular eruptions when applied to the skin. The active vesicant and cathartic principle is a croton resin, $C_{15}H_{22}O_4$, which is free in the oil, consequently it exerts its effect in both the stomach and intestines. One drop of croton oil is a full dose for man.

Croton oil is a drastic cathartic, causing copious movements after an hour or two. Pain and nausea are frequently connected with its administration. Large doses produce symptoms of severe gastroenteritis. A drop of the oil on the skin for an hour may cause a pustule. It was formerly taught that the action is due to an acid and that it acted in the same way as castor oil, but the active ingredient is a resin, which can be isolated. Oil deprived of the resin is inactive. It is too drastic for practical use and has been deleted from the U. S. P.

ANTHRACENE CATHARTICS

The principal members of the anthracene group of cathartics are cascara, senna, rhubarb, and aloes. They are also known as the emodin cathartics since the substance, emodin, is the most important derivative and is found in all of the drugs of this group. Other derivatives are also present which explains individual properties and activity of each of the members. These active principles are absorbed in the intestine to some extent and excreted in body fluids (milk and urine). Some are responsible for the color of the urine (a yellowish brown if the reaction is acid or a reddish violet if the urine is alkaline).

The anthracenes exert their main action on the large bowel, hence have a tendency to produce griping. They require from six to twelve hours or more to produce evacuation.

Cascara

Cascara Sagrada is obtained from the bark of the tree *Rhamnus purshiana*. It was once called "sacred bark" by the Indians of the Pacific Coast region. It is one of the most extensively used of all

the cathartics. Its action is comparatively mild and is less likely to cause griping than some of the other anthracene derivatives. Cascara contains a bitter and a nonbitter cathartic principle, both of which are therapeutically active. The bitter principle has been removed in the aromatic fluidextract, hence the dosage must be twice as much as in the plain fluidextract.

Although cascara is classed with the cathartics which act by irritation, it is particularly useful because it acts upon intestinal musculature and improves its tone. It is used chiefly for habitual constipation, for as the normal tone of the bowel is regained the drug can be withdrawn.

Aloe

Aloe is the dried juice of leaves of a plant which grows in Africa and the West Indies. The active principle, aloin, is a glucoside which is changed in the intestine to a substance that causes it to be classed with this group of cathartics. Aloe is the most irritating of the emodin cathartics. In large doses it is said to cause pelvic congestion and is accompanied by considerable griping. It is a constituent of a number of cathartic preparations as in A.B.S.C. pills in which the A stands for aloin, B for belladonna, S for strychnine, and C for cascara. Several other preparations are mentioned in the summary of preparations.

Rhubarb

Rhubarb is obtained from the dried roots of several species of rheum which grows in China. Although it resembles our garden rhubarb, the latter has no cathartic action. This drug contains tannin and hence an astringent action accompanies and sometimes overshadows the cathartic action. It is not accompanied by severe griping and discomfort.

Senna

Senna is obtained from the dried leaves of the *Cassia senna* plant, a cathartic well known to the Arabians. The dried leaves have been used to make a home-made infusion of the drug which is decidedly potent. It produces a thorough bowel evacuation in from four to six hours and is likely to be accompanied by griping.

Preparations of Anthracene Cathartics.—

Extract of Cascara Sagrada (Extractum Cascarae Sagradae), U. S. P.

Dose: 0.3 Gm. (5 grains) orally.

Cascara Sagrada Extract Tablets (Tabellae Cascarae Sagradae Extracti), U. S. P. Dose: 0.3 Gm. (5 grains) orally.

Compound Pills of Cascara (Pilulae Cascarae Compositae; Hinkle's Pills), N. F. Dose: 1 pill.

Fluidextract of Cascara Sagrada (Fluidextractum Cascarae Sagradae), U. S. P. Dose: 1 cc. (15 minims) orally.



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Extract of Cascara Sagrada (Extractum Cascarae Sagradae), U. S. P.

Dose: 0.3 Gm. (5 grains) orally.

Cascara Sagrada Extract Tablets (Tabellae Cascarae Sagradae Extracti), U. S. P. Dose: 0.3 Gm. (5 grains) orally.

Compound Pills of Cascara (Pilulae Cascarae Compositae; Hinkle's Pills), N. F. Dose: 1 pill.

Fluidextract of Cascara Sagrada (Fluidextractum Cascarae Sagradae), U. S. P. Dose: 1 cc. (15 minims) orally.

Aromatic Fluidextract of Cascara Sagrada (Fluidextractum Cascarae Sagradae Aromaticum), U. S. P. Dose: 2 cc. (30 minims) orally.

Aloe, U. S. P. Dose: 0.25 Gm. (4 grains) orally. It is used as a constituent of pills.

Aloin (Aloinum), U. S. P. Dose: 15 mg. ($\frac{1}{4}$ grain) orally. Aloin is a mixture of active principles obtained from aloe. It is intensely bitter and is used as a constituent of pills.

Pills of Aloin, Strychnine, and Belladonna (Pilulae Aloini, Strychninae, et Belladonnae), N. F. (A, B, S pills).

Aromatic Syrup of Rhubarb (Syrupus Rhei Aromaticus), U. S. P. Dose: 10 cc. (2½ drams), orally.

Fluidextract of Senna (Fluidextractum Sennae), U. S. P. Dose: 2 cc. (30 minims) orally.

Syrup of Senna (Syrupus Sennae), U. S. P. Dose: 8 cc. (2 drams) orally.

Compound Senna Powder (Pulvis Sennae Compositus, Compound Licorice Powder), N. F. Dose: 4 Gm. (1 dram) orally. The powder contains senna, glycyrrhiza (licorice), washed sulfur, oil of fennel, and sugar.

Senna tea is an infusion of senna leaves made from a teaspoonful of leaves to a cup of hot water. Senna is sometimes cooked with equal parts of prunes or figs and the mixture is given as a purgative.

Phenolphthalein

This phenol derivative is a synthetic substance whose cathartic action is similar to that of the anthracene group. It is a white powder insoluble in water but soluble in the juice of the intestine where it exerts its relatively mild irritant action. Evacuation is produced in from eight to twelve hours unaccompanied by griping. It acts upon both the small and large bowel, particularly the latter. When given orally, part of the drug is absorbed and resecreted into the bile. When given parenterally, large amounts are secreted into the bile and thus a prolonged cathartic action may be obtained.

Repeated doses may cause nausea and in some susceptible individuals a skin rash may appear. In other cases a prolonged and excessive purgative effect may indicate individual idiosyncrasy. Obviously susceptible individuals should avoid the use of phenolphthalein. However, because the drug is odorless and tasteless and relatively pleasant to take, it is found in a number of proprietary preparations and is sold in candy form and in a chewing gum. Care needs to be exercised in preventing children from getting these preparations, as they are likely to regard them as ordinary candy or gum and may thus get an overdose of the drug. Deaths have been reported from such accidents, although the toxic dose is large.

Preparation.—

Phenolphthalein (Phenolphthaleinum), U. S. P. Dose: 60 mg. (1 grain) orally.

It is combined in many proprietary cathartics along with agar, liquid petrolatum, and other irritant cathartics.

Mild Mercurous Chloride (Calomel)

All preparations of mercury are irritant to the gastrointestinal tract and cause catharsis. The soluble preparations and those that are readily converted into soluble preparations in the body are too irritant and toxic for practical use. Consequently, preparations of the metal and the mild chloride are used as cathartics.

Calomel at one time was a very popular purgative and was used especially for the relief of biliousness because it was thought to stimulate bile formation and excretion from the liver and also to act as a purgative. Subsequent investigation has not only failed to show that calomel has this effect in the liver but also that it is not without serious toxic manifestations. Its popularity has consequently decreased.

Judged from fluoroscopic observation, calomel acts mainly on the duodenum and small intestine; much less on the colon. This hastens the contents along to the colon and, it is thought by some, also prevents absorption. Large doses may cause griping from an action on the colon.

The stool after calomel may be highly colored with green-colored bile. This is believed to be due to the antiseptic action of the bile which inhibits the action of the bacterial flora which ordinarily bring about the reduction of the green bile pigment.

Calomel passes through the stomach unchanged, but in the intestine a part of the mercurous chloride is changed into mercuric oxide which is somewhat soluble. The mercuric ion irritates the intestinal mucosa to the extent that much of the drug is swept out of the bowel unchanged. The soluble mercuric ions are absorbed and are responsible for a diuretic action in the kidneys. If for some reason the drug is delayed in the intestine, sufficient absorption may take place to cause the following toxic symptoms: abdominal cramps with severe diarrhea, oliguria, anuria, hematuria, shock, and metallic taste in the mouth. It is therefore contraindicated in cases of possible intestinal obstruction or any condition likely to cause delayed passage through the bowel. Salines are frequently given after calomel to insure its complete removal from the bowel. There are many safer and better cathartics to use than calomel.

Preparations.—

Mild Mercurous Chloride (Hydrargyri Chloridum Mite), U.S.P. (Calomel). Dose: 0.12 Gm. (2 grains) in divided doses.

Compound Pills of Mild Mercurous Chloride (Pilulae Hydrargyri Chloridi Mitis Compositae, Compound Cathartic Pills), N.F. Dose: 2 pills. This preparation contains a number of drastic cathartics and calomel. Infrequently used.

The Jalap, Drastic or Resin Group

Drastics are violent purgatives which in large doses produce severe gastritis and enteritis, and often nephritis and cystitis. The irritant action may be illustrated on the skin and mucous membranes of the eye, nose, and throat. In the eye a little of the powdered drug or a solution causes redness and the symptoms of inflammation. If applied to the nose and throat, sneezing and coughing quickly develop. When solutions are injected intravenously or subcutaneously, enteritis and nephritis develop as when given by mouth.

This group includes jalap, scammony, podophyllin, colocynth, and elateria. They are mostly of uncertain composition but owe their action mainly to resins. Oleum Tigllii is also a drastic cathartic (see Cathartic Oils).

There has been much discussion concerning the necessity of bile for the action of these purgatives. No unanimity of opinion has been reached; it seems that bile is not absolutely necessary but its presence increases activity, probably due to its solvent action on the resinous active constituents.

The Site of Action.—These drugs begin to stimulate the gastrointestinal tract as soon as they reach the stomach and they act in all parts of the intestine. They may cause nausea and vomiting. The action does not attain a maximum until it reaches the lower part of the small intestine. This seems due to the solvent action of the gastrointestinal contents which does not reach a maximum until the drug has been exposed for some time. They all produce increased peristalsis and colic in the large intestine and at the same time hyperemia and reflex stimulations of all pelvic organs. In some conditions, therefore, they may be decidedly dangerous.

Because of the drastic action little time is given for the absorption of fluids from the intestine; consequently, less inflammatory reaction takes place than if the drug were delayed in action. Delayed passage permits increased absorption and irritation of the kidneys.

Therapeutic Uses.—Because of their irritant action this group of drugs should be limited to cases which do not respond to the milder cathartics. For the most part they are little used for sick people because of their severe action. Overdosage leads to fall in blood pressure, collapse and gastroenteritis. They are contraindicated during menstruation and pregnancy, in patients with nephritis, enteritis, or hemorrhoids, and in old age or conditions of low vitality. It is questionable whether any of this group is superior to the milder acting cathartics.

Preparations.—

Compound Jalap Powder (Pulvis Jalapae Compositus), N.F. Dose: 2 Gm. (30 grains) orally.

Resin of Podophyllum (Resina Podophylli), N. F. Dose: 10 mg. ($\frac{1}{6}$ grain).

Compound Cathartic pills mentioned under calomel contain in addition to calomel—jalap, colocynth, and gamboge.

Cathartics Which Act by Stimulating the Neuromuscular Mechanism

1. **Pituitrin.**—Pituitrin is obtained from the posterior lobe of the pituitary glands of animals. Extracts of this gland when given parenterally have three types of action. They cause contraction of smooth muscle in the blood vessels and intestine (pressor effect); they stimulate contraction of uterine muscle (oxytocic effect); and they act upon kidney structures so as to increase the reabsorption of water (antidiuretic action). We will consider the pressor effect in this chapter as it is related to cathartic action.

It has been found that the pressor principle stimulates the musculature of the small intestine and the colon resulting in marked peristaltic contractions. The motility seems to be increased without causing a change in tonus. Preparations of posterior lobe pituitary have been found useful in the treatment and prevention of post-operative gas pains, intestinal paralysis, and tympanites.

Preparations.—

Posterior Pituitary Injection (Injectio Pituitarii Posterioris), U. S. P. Dose: 1 cc. (15 minims) hypodermically. This preparation contains both the pressor and the oxytocic principles.

Ampoules of Pitressin, N. N. R. Dose: 0.3 to 1 cc. (5-15 minims) intramuscularly. This is an aqueous solution containing the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland.

The usual dosage is 1 ampoule or minims 15. When the preparations of solution of posterior pituitary are marked surgical or obstetrical, it refers to the strength of the solution, the former being twice as strong as the latter.

Posterior pituitary extracts must be administered parenterally because they are destroyed in the gastrointestinal tract when taken by mouth. The usual method of administration is subcutaneously or intramuscularly.

2. **Physostigmine.**—Physostigmine salicylate is sometimes used to stimulate intestinal peristalsis in paralytic forms of constipation or for severe tympanites. One to two milligrams may be given hypo-

dermically. Prostigmine has come to be preferred by some physicians. Doses which are effective as cathartics border on the toxic dose, and the patient should be watched closely for signs of toxicity. Physostigmine acts after absorption and prolongs the effect of acetylcholine by the inhibition of cholinesterase.

ANTIDIARRHEICS

Diarrhea is a symptom of a disorder of the bowel associated with too rapid a passage of intestinal content, frequent fluid stools, and griping. The remedies used to check diarrhea are determined by the causes which often are numerous. Some of the common causes are (a) contaminated or partially decomposed food, (b) intestinal infection of bacterial or protozoan origin, (c) nervous disorders, (d) sudden changes in temperature, (e) circulatory disturbances, (f) disturbed gastric physiology, such as absence of hydrochloric acid, (g) inflammatory processes of adjacent viscera.

In view of the numerous possible causes, it is evident that the treatment must vary greatly. The fundamental principle is to remove the cause. In some cases a cathartic which brings about the emptying of the entire bowel may be the means of relieving the diarrhea by removal of the irritating material. In protozoan infections such as amoebic dysentery, the treatment must be directed toward killing the offending organism. The correct treatment of a specific case, therefore, depends on a correct diagnosis.

The drugs used in the treatment of diarrhea include (1) *demulcents*, (2) *antiseptics*, (3) *carminatives*, (4) *sedatives*, (5) *astringents*, and (6) *adsorbents*.

1. The demulcents in common use are salts of bismuth, calcium carbonate, and magnesium oxide. They have a soothing effect on the irritated membrane of the gastrointestinal tract. Some demulcents are old household remedies, such as boiled starch, gruel, and barley water.

Bismuth preparations are used internally as protectives to coat over the stomach and intestines and to check gastritis and diarrhea. They act mechanically like a dusting powder. The salts used are:

Bismuth Subcarbonate (Bismuthi Subcarbonas), U. S. P. Dose: 0.5-2 Gm. (8-30 grains) every two to three hours.

Bismuth Subnitrate (Bismuthi Subnitrates), N. F. Dose: 1 Gm (15 grains) every two or three hours

Precipitated Calcium Carbonate (Calcii Carbonas Praecipitatus), U. S. P. Dose: 1 Gm. (15 grains).

2. **Intestinal Antiseptics.**—It is of course impossible to disinfect the intestinal tract, nor would it be practical to do so, but it is frequently necessary to reduce the number of harmful organisms. Two of the sulfonamide drugs—sulfaguanidine and sulfasuxidine (succinyl-sulfathiazole)—exert a marked bacteriostatic effect in the intestine against certain bacterial organisms. They are prescribed in the treatment of acute and chronic bacillary dysentery. Other and older preparations include methylene blue, gentian violet, and salol. Certain arsenicals and emetin are used to kill the organisms causing amoebic dysentery and thus relieve the associated diarrhea.

3. **Carminatives.**—A number have been mentioned earlier in this chapter.

4. **Intestinal sedatives** most commonly used are preparations of opium in the form of paregoric, laudanum, or an opium derivative such as papaverine hydrochloride. Belladonna and its alkaloids, either natural or synthetic, are also used for their antispasmodic action on the smooth muscle of the intestine.

5. **Astringents** used in the gastrointestinal tract are drugs which cause shrinking of the mucous membranes or raw tissues.

a. **Tannic Acid.**—The main active ingredient of all vegetable astringents is tannic acid. A large number of drugs owe their action to this principle. When drugs containing tannin are taken into the mouth, they cause a feeling of constriction, roughness, dryness and the characteristic harsh, bitter, astringent taste, and often a visible wrinkling of the mucous membranes to which they are applied.

In the intestine it acts both by combining with and precipitating protein material and by diminishing mucous secretions of the intestine by precipitating a protecting layer on the intestinal wall. As a result of both actions the peristaltic reflex and intestinal movements are retarded so that more time is given for absorption of fluids.

When given orally it is best given in an encapsulated form since it may otherwise cause gastric irritation, nausea and vomiting.

Preparation.—

Tannic Acid (Acidum Tannicum), U. S. P. Dose: 15 grains.

To avoid the astringent action on the stomach and yet procure the astringent intestinal action, numerous combinations of tannin have been prepared. The best known are acidum acetyl tannicum (diacetyl tannic acid), tannoform (formaldehyde tannin), tannopin (methenamine tannin), and tannalbin (egg albumen tannate).

b. The bismuth salts, as mentioned under **Demulcents**, are also given for their astringent action.

6. **Adsorbents** may be given to relieve diarrhea which in turn may be caused from gaseous distention of an irritated bowel.

a. **Activated Charcoal** (*Carbo Activatus*), U. S. P., is the residue prepared from various organic materials and treated to increase its absorptive power. It is fine, black, odorless, and tasteless.

In a dry state charcoal is one of the most effective adsorbent substances, being able to adsorb 35 times its volume of carbon dioxide and 90 times its volume of ammonia.

Dose: 1 Gm. (15 grains).

b. **Kaolin**, N. F., a naturally occurring aluminum silicate, long used in China for the relief of diarrhea. It is given suspended in water in doses of 50 to 100 grams every three or four hours until relief is obtained. Its action is like that of charcoal—adsorbent.

Kaopectate (Upjohn) contains kaolin and pectin and is used as an adsorbent and demulcent.

ANTHELMINTICS

Anthelmintics are drugs used in the treatment for worms. *Ver-micides* are drugs which bring about the death of the worm while *vermifuges* are supposed to narcotize and expel the worm from the intestinal tract. This classification is, however, too arbitrary since factors of dosage and individual response greatly determine the effect.

Most anthelmintics are toxic to man as well as to the parasite. A good anthelmintic is one which has a minimum toxic effect on the host and a maximum toxic action on the parasite.

Classification of Worms.—The majority of the human race, living especially in tropical and subtropical climates, is infected with worms of one species or another. These infections are of two classes:

A. Those in which the worm lives in the alimentary canal. The most important of these worms are the (1) tapeworms (*taenia* and *bothriocephalus*), (2) roundworms (*ascaris*), (3) threadworms (*oxyuris*), (4) hookworms (*ancylostoma* and *necator*).

B. Those in which the worm lives in the tissue of the host. (1) *Bilharzia* (*Schistosomum haematobium*) lives in the portal vein and discharges ova which pass into the bladder and gut, causing inflammation of these organs and loss of blood per rectum. (2) *Filaria*. The adult worm lives in the tissues, often in the subcutaneous tissues, and discharges ova which live in the blood stream and lymphatics. Among other effects it causes elephantiasis.

The use of anthelmintics (*anti*, against; *helminthos*, worms) is the most primitive type of chemotherapy. Hundreds of vegetable substances were formerly used; relatively few have been retained. A few new synthetic drugs are rapidly replacing some of the older preparations.

Dangers Associated With Worm Infestations.—

1. Worms may cause mechanical injury to tissues and organs, e.g., roundworms when present in large numbers may cause intestinal obstruction; filariae may block lymphatic channels, hookworms often cause extensive damage to the wall of the intestine and cause considerable loss of blood.

2. The patient may absorb toxic materials made by the parasite.

3. The tissues of the host may become traumatized and their resistance to other infection seriously depleted.

4. Heavy infestation of worms will rob the host of food. This would be particularly significant in children.

Factors to Be Considered in Choice of an Anthelmintic.—

1. The cost of the drug.

2. Ease of administration.

3. The relative safety and efficiency of the anthelmintic.

Intelligent treatment of the patient requires a knowledge of (1) the type of worm or worms which are present; (2) the drug which is the best anthelmintic for the type or types of parasites involved; (3) the method of determining the effectiveness of the treatment.

Although the technic of treatment necessarily varies with the drug used the maximum effects are often secured when the intestinal tract has been well emptied before the drug is given and well evacuated afterwards. The dose varies with the general condition of the patient, the size, age, and sex.

Aspidium, *Filix-Mas* (Male Fern)

The male fern is one of the oldest known and most used anthelmintic agents. The species from which the official drug is obtained is the *Dryopteris filix-mas*, a fern commonly found in England. The anthelmintic action is due to the presence of several closely related substances, i.e., filicic acid, filmaron, etc. *Aspidium* is a useful drug for the removal of the tapeworm from the intestinal tract but is not of value in the removal of other types of worms.

Action.—*Aspidium* acts as an irritant in the gastrointestinal tract. Large doses bring about stimulation of the spinal cord which may be

followed by an ascending depression of the nervous system until involvement of the respiratory center in the medulla brings about respiratory failure. Muscle tremor is sometimes observed and the drug exhibits an affinity for the optic nerve which may cause visual disturbance and blindness. Large doses depress the myocardium and weaken the force of the heart. Smooth muscle is also depressed and this probably explains its anthelmintic action, i.e., the smooth muscle of the worm is paralyzed and thus it is possible to expel the worm by means of a cathartic.

A certain amount of the drug is absorbed although an aim in administration is to avoid as much absorption as possible. That which is absorbed is excreted in the urine.

Symptoms of Poisoning.—Dangerous symptoms of poisoning follow the absorption of the active constituents of aspidium. Toxic symptoms may occur even with moderate doses and large doses are often dangerous although not uniformly so. The milder symptoms include headache, dizziness, diarrhea, and nausea. More severe symptoms include yellow vision, dyspnea, convulsions, severe diarrhea which may become bloody, colic, vomiting, albuminuria, jaundice, and sometimes death from respiratory or cardiac failure.

In case of recovery the progress is slow and the blindness may be permanent.

Treatment must be symptomatic. Saline cathartics are given to help rid the bowel of the drug and decrease absorption, sedatives to control convulsions, and respiratory stimulants as indicated.

Contraindications.—Aspidium should be avoided when the patient is pregnant, weak and debilitated, or suffers from disease of the liver or kidney or has any ulceration or inflammatory condition along the gastrointestinal tract. It should also be avoided in children if possible, since children seem to be especially susceptible to the toxic effects of aspidium.

Administration.—A fat-free diet for a day or two before the aspidium is given is recommended because the presence of fat in the intestine promotes the absorption of the drug. Lunch and supper are omitted the day before the treatment and a saline cathartic is given the evening before the treatment. (Magnesium sulfate, 15 grams in water.) The aspidium is administered the next morning on an empty stomach in divided doses, one hour apart. Since the taste is very bitter and difficult to disguise it is best given in capsules. A saline cathartic is again administered two hours after the last dose and two hours later a large soapsuds enema is given to insure removal of all of the drug.

The nurse must make certain that all parts of the stool are saved. Failure to do this may mean that the treatment has been in vain, for unless the head of the worm is found there is absolutely no assurance that the treatment is successful.

Preparation.—

Oleoresin of Aspidium (*Oleoresina Aspidii*), U. S. P., a thick green liquid. Dose: 4 Gm. (60 grains) in capsules or emulsion.

Thymol

Thymol or thyme camphor occurs in the volatile oils of several plants, especially in thyme. Its most important use is in the treatment of hookworm infection. Thymol is readily soluble in alcohol and in olive oil. In the treatment of hookworm with thymol, an adult is given about 2 Gm. in divided doses. The treatment is more effective if the patient fasts for about twelve hours before thymol is given. The dose is divided into three portions and given about an hour apart. Two hours after the last portion, a strong saline purgative is given to clear the organisms from the gut, and to prevent further absorption of thymol. Thymol has to a great extent been replaced by less toxic and equally efficient drugs. It is still used, however.

Preparation.—

Thymol, U. S. P. Dose: 2 Gm. (30 grains) divided into three doses.

Pelletierine

Pelletierine is a mixture of alkaloids obtained from the bark of the pomegranate, which grows principally in India and North Africa. Pomegranate has been used from time immemorial as a vermicide and is mentioned by Pliny and Dioscorides.

Action.—Pelletierine first stimulates and then depresses the nervous system. Like aspidium it exerts a selective action on the optic nerve. Its action on voluntary muscle resembles curare, i.e., it paralyzes voluntary muscle, when sufficient drug is given. It has a great effect on tapeworms, especially the pork tapeworm but slight effect on other worms.

Symptoms of Poisoning.—The ordinary dose may produce mild toxic symptoms: vertigo, dimmed vision, weakness, cramps in the legs, headache, prostration, etc., and sometimes convulsions. Paralysis eventually develops which may involve the muscles of respiration and cause death. Treatment involves removal of the drug with

a saline cathartic, artificial respiration, and measures according to the needs of the patient.

Administration.—The patient is prepared in the same way as for the administration of aspidium. It should be avoided in all but robust adults.

Preparation.—

Pelletierine Tannate, N. F. Dose: 0.25 Gm. (4 grains).

Oil of Chenopodium (American Wormseed)

Oil of Chenopodium or Oil of Wormseed is a volatile oil from the flower and fruiting plant *Chenopodium ambrosioides*. It is useful in ridding the intestine of hookworms and roundworms. It is also effective against the dwarf tapeworm.

Action.—Oil of chenopodium is irritating to the mucosa of the gastrointestinal tract. The oil has a burning taste and brings about reflex stimulation of the gastric and salivary glands. Smooth muscle of the bowel is depressed, and constipation is likely to result unless a cathartic is given. Its anthelmintic action is due to its action on the muscle of the worm. Chenopodium also affects the nervous system by first stimulating it and then depressing it to the extent that unconsciousness may result. Death is due to depression of the vasomotor center and the cardiac muscle.

Symptoms of Poisoning.—Large therapeutic doses may cause the following symptoms: dizziness, nausea and vomiting, and impaired vision. Toxic doses of the drug may produce severe depression, unconsciousness, and slow respiration. The drug is also toxic to the kidney and the liver causing albumin and blood to appear in the urine and jaundice in the skin. Treatment is largely symptomatic.

Administration.—Chenopodium is usually administered in gelatin capsules in divided doses one hour apart. The patient is not purged nor made to fast, as it is now thought that such a procedure only weakens the patient and does not increase the vulnerability of the parasite. A high carbohydrate diet a few days before the treatment increases the glycogen store in the liver and diminishes the toxic effect of the drug on the liver. A saline cathartic is administered one hour after the last dose of the drug. Some authorities advise giving castor oil as the cathartic to decrease toxic effects of the chenopodium.

Preparation.—

Oil of Chenopodium (*Oleum Chenopodii*), N. F. (Oil of American Wormseed). Dose: 1 cc. (15 minims) in capsules.

The main disadvantage of chenopodium is that its margin of safety is not large. A single dose of the drug, however, may remove 90 to 95 per cent of roundworms which infest the patient.

Santonin

Santonin is also a very old anthelmintic. It is secured from the *Artemisia* plants (Levant Wormwood) which are widely distributed.

Action.—Santonin is one of the simplest anthelmintics to administer because it is tasteless and nonirritating. The drug depresses a number of the special sensory centers, those of hearing, taste, smell, and color vision. Large doses cause stimulation of the central nervous system which is followed by depression. Toxic doses produce cardiac depression.

The drug is particularly effective against roundworms. The worms are irritated and migrate from the small intestine into the large bowel from which they are expelled.

Symptoms of Poisoning.—The production of "yellow vision" is one of the earliest and mildest of the toxic symptoms. More severe symptoms include headache, vomiting, diarrhea, confusion, and skin rash. These may be followed by a drop in temperature, muscle tremor, and convulsive seizures. Renal irritation is made evident by the presence of blood and albumin in the urine. Treatment is supportive and symptomatic.

Administration.—Santonin is given once daily for two or three days. The dose is usually given after the evening meal and followed by a purgative in the morning. It should not be given on an empty stomach because of the enhanced absorption.

Preparation.—

Santonin (Santoninum), N. F. Dose: 60 mg. (1 grain).

Carbon Tetrachloride

Carbon Tetrachloride is a clear colorless liquid having an odor which resembles chloroform and little or no taste. It is an effective anthelmintic, especially against hookworm, but it also removes other intestinal parasites, such as *Oxyuris vermicularis*, *Ascaris lumbricoides* and *Trichocephalus dispar* (pinworms, roundworms, and whipworms), but it is less effective against the latter types than certain other drugs. It is reported that about 95 per cent of the hookworms are removed by the first dose of carbon tetrachloride and occasionally all are removed. It has an added advantage of being relatively inexpensive.

Action.—Carbon Tetrachloride has narcotic and anesthetic properties similar to those of chloroform. When applied to the skin it acts as an irritant. In the mouth it has a pungent burning taste, and in the stomach it causes a feeling of warmth. Intestinal peristalsis is increased due to irritation.

Unless large amounts gain access to the circulation, systemic effects on the nervous system and on the heart are not observed. Fats and alcohol increase the amount of absorption and hence are to be avoided when this drug is administered.

Symptoms of Poisoning.—Acute symptoms of poisoning may appear if there has been much absorption of the drug. These are headache, sleepiness, nausea and vomiting, abdominal cramps, and diarrhea. Convulsive seizures are not uncommon. With continued absorption a progressive depression develops, and death may result from cardiovascular collapse. Some of the ill-effects may be delayed. Autopsy findings indicate that carbon tetrachloride has a specific toxic effect on the liver and kidneys. Although on the whole, carbon tetrachloride appears as a fairly safe vermifuge, serious toxic symptoms do occur and even death has been reported especially in patients addicted to the use of alcohol. Special precautions should accompany the administration of the drug.

Administration.—The diet prior to the administration of carbon tetrachloride should be high in carbohydrates and calcium and low in fat and meat. The evening meal should be light and the drug administered in a capsule form the next morning before breakfast. The patient should be cautioned not to bite the capsule as the drug may then be inhaled. A saline purgative should follow within two or three hours. Alcohol, oils, or fats should not be taken during the treatment. In cases of calcium deficiency, intravenous administration of calcium salts alone or with glucose may help to prevent toxic reactions.

Preparation.—

Carbon Tetrachloride (Carbonei Tetrachloridum), N. F. Dose: adults, 2.5 cc. (40 minims). Not to be repeated for three weeks

Tetrachloroethylene

Tetrachloroethylene is a liquid preparation which closely resembles carbon tetrachloride and may come to replace the latter drug as an anthelmintic. It is less soluble in water and less easily absorbed from the intestinal tract than carbon tetrachloride. This fact prob-

ably explains why it appears to be less toxic to the liver and kidneys. It is as effective as carbon tetrachloride in the treatment of hookworm but not particularly effective against other intestinal parasites. It may cause some dizziness and drowsiness but no serious symptoms of poisoning or deaths have been reported. It is as efficient as carbon tetrachloride and definitely less toxic but somewhat more expensive.

Administration.—The general preparation of the patient is much the same as for the administration of carbon tetrachloride. The drug is usually given in a soft gelatin capsule and followed after a few hours with a saline purgative. Fats, oils, and alcohol should be avoided during the treatment. One dose of the drug may prove sufficient but if not, further administration should be delayed for a week or ten days.

Preparation.—

Tetrachloroethylene (Tetrachloroethylene), U. S. P. Dose: 3 cc. (45 minims).

Hexylresorcinol

Hexylresorcinol is a synthetic derivative of resorcinol which was introduced into medicine as a urinary antiseptic. It is also rather extensively used as an anthelmintic. It is effective against a number of worm infestations including hookworm, pinworm, dwarf tapeworm, and whipworm.

Action.—Hexylresorcinol is an antiseptic which has a phenol coefficient of 45. Its action is due in part to its ability to lower surface tension. Following oral administration, part of the drug is excreted in the feces unchanged and a part of it is absorbed. The part absorbed is excreted in a conjugated form by the kidney.

Symptoms of Poisoning.—Hexylresorcinol when applied in high concentration is irritating to tissues. Oral administration may cause irritation along the gastrointestinal tract. Systemic toxicity, however, is low, which is explained on the basis of its limited absorption.

Administration.—The drug (in gelatin capsules) is administered in the morning on an empty stomach. It is important not to break the capsule in the mouth as extensive irritation may be caused. The dose should be followed two hours later with a saline cathartic. The treatment may be repeated in three days if necessary.

Hexylresorcinol is not only effective against a number of different worm parasites but it has also the advantages of low toxicity and mildness so that it can be used for children and patients for whom the more drastic anthelmintics are contraindicated.

Preparation.—

Hexylresorcinol (Hexylresorcinol), U. S. P. Dose: 1 Gm. (15 grains) in capsules.

THERAPEUTIC RÉSUMÉ

1. For roundworms, *Ascaris lumbricoides*, and for whipworms, *Trichocephalus dispar*, the remedy most used is oil of chenopodium. Other remedies, such as carbon tetrachloride, santonin, hexylresorcinol, pumpkin and squash seeds, are also employed.
2. Pin- or threadworms. These do not cling to the intestinal wall and may be washed out with cathartics or enemas. As enemas, infusion of quassia, limewater, kerosene, 1 per cent tannic acid, 1:2000 quinine sulfate, soapsuds containing 1 ounce of oil of turpentine, and other solutions are used. The anal region should be kept clean and may be treated with an antiseptic ointment such as yellow oxide of mercury. By mouth, oil of chenopodium, sulfur, and thymol have some value, but are not dependable. It is imperative to prevent reinfection if the condition is to be successfully treated.
3. Against hookworms—carbon tetrachloride, thymol, tetrachlorethylene, hexylresorcinol.
4. Against tapeworms—oleoresin aspidium, or pelletierine tannate
5. Against bilharziasis, antimony and sodii tartras, is less toxic than the potassium salt and has replaced it for intravenous injections. Dose: $\frac{1}{2}$ grain, increasing to 2 grains three times a week. A long, continued course may be necessary.

Amoebiasis

Amoebiasis or amoebic dysentery is a disease that may be acute or chronic, caused by *Endamoeba histolytica*. There is a special liability to the formation of abscesses in the liver. The parasite occurs in two forms, the active form and the resting or cystic form. This distinction is important because the cystic form is much more resistant to treatment. In chronic cases the cystic form always occurs, and it is said by men of experience that complete cure has not yet been accomplished. Most of the remedies reduce the infection to a low level so that the patient's natural power of resistance can keep in check the parasites that remain in the body after treatment. Others believe a complete cure may be effected, but a cure may require several courses of treatment. The most important drugs used in the treatment of amoebiasis are ipecacuanha and its alkaloid,

emetine; organic pentavalent arsenic compounds, such as carbarsone and acetarsone (stovarsol); also the iodohydroxyquinoline compounds, vioform and chiniofon (Yatren).

Ipecac (Ipecacuanha)

Ipecac is the dried root of *Cephaelis ipecacuanha*, a perennial shrub growing in Brazil and other South American states. It contains several alkaloids in which two, *emetine* and *cephaeline*, have an emetic action. Ipecac is extensively used as an expectorant and is a constituent of Dover's powder.

Amoebicidal Action.—Ipecac has long been used empirically in the treatment of amoebic dysentery. It acts specifically on the causative organism, the amoeba, as does quinine on the malarial organism. Formerly the powdered ipecac was used, but because of difficulties in administration and because it produces gastrointestinal irritation, it is now rarely used unless the patient does not respond to the more modern methods of treatment.

Emetine

Emetine hydrochloride when given hypodermically in less unpleasant and more effective than ipecac given by mouth. Its mode of action has been disputed, but it apparently has a direct lethal action on the *Endamoeba histolytica*.

It is readily absorbed from the parenteral site of administration but is rather slowly excreted. It may therefore produce cumulative effects in the tissues.

Uses.—The main use of emetine is to control the symptoms of acute amoebic dysentery or the symptoms which may suddenly appear during chronic states of the disease. It is also of value in the treatment of amoebic abscesses and amoebic hepatitis. It should not be given to patients with mild symptoms or to carriers since the drug does not destroy the encysted form of the parasite.

Symptoms of Poisoning.—Emetine is a general protoplasmic poison. It is slowly excreted and may give rise to cumulative toxic reactions. Degenerative changes in the liver, heart, kidneys, and muscles may occur. Heart changes may vary from disturbance in rhythm to acute myocarditis and heart failure. Other symptoms of poisoning include dizziness, nausea and vomiting, and severe diarrhea. Emetin is contraindicated in patients with heart or kidney disease, during pregnancy, and in children.

Administration.—Emetine is best administered when the patient is at bed rest and under direct medical supervision. Toxic symptoms must be carefully watched for and the drug discontinued if they appear. The blood pressure should be checked at least once a day.

The drug is preferably given by the intramuscular route although the subcutaneous route is also recommended. Treatment is usually followed by rapid disappearance of symptoms, but further treatment with one of the other amoebicides is usually indicated.

Preparation.—

Emetine Hydrochloride (Emetinae Hydrochloridum), U. S. P. Dose: 60 mg. (1 grain).

Pentavalent Arsenic Compounds Used in Amoebiasis

Acetarzone (Stovarsol), N. F., contains 27.1 to 27.4 per cent arsenic. It is the first of these compounds for which the claim is made that it will act when given orally. Its use in amoebic dysentery is undoubtedly of value, though it is apparently more toxic than carbarsone. It is of value especially in chronic cases that have resisted emetine. It is also used in the treatment of trichomonas vaginitis. Since it contains arsenic, it may give rise to gastrointestinal symptoms, hepatitis, and cutaneous eruptions. At the least sign of intolerance its use should be discontinued. Excretion is relatively slow and cumulative effects may arise. It should not be used where there is kidney or liver damage. Some think that the effective dose is unduly toxic and recommend carbarsone. Dose: orally, 0.25 Gm (4 gr.) two or three times a day for seven days

Carbarsone (Carbarsonum), U. S. P. (paracarbamido, phenyl arsenic acid) contains about 28 per cent arsenic. In the treatment of amoebiasis it is usually administered by mouth. It is said to be less toxic than acetarzone, and while serious toxic effects are uncommon, cutaneous eruptions and other reactions common to arsenic have been observed. Like other arsenic compounds, it should not be used where there is kidney or liver pathology. While visual disturbances appear to be rare, the possibility of injury to the optic nerve must be kept in mind during the use of the drug. Excretion is relatively slow, with a tendency to cumulative effects; rest periods should be part of the treatment in order to avoid these effects.

Dosage.—Orally, for adults, 0.25 Gm. (4 gr.) twice a day for ten days. If necessary, this may be repeated after a ten-day rest period.

For children, the dosage must be reduced according to age. For retention enemas, 2 Gm. (30 gr.) of the drug dissolved in 200 cc. of warm 2 per cent sodium bicarbonate may be administered, followed by a cleansing enema every other night for a maximum of 5 doses. Oral administration should be interrupted during this period.

Iodoxyhydroxyquinoline Compounds

Chiniofon (Chiniofonum), U. S. P. (Yatren). Chiniofon is an oxyquinoline derivative containing not less than 26.5 per cent and not more than 28 per cent of iodine. The action of this drug in amoebic dysentery is probably due to its absorption and direct action on the amoebae in the bowel wall. The drug has been reported to cause diarrhea, but serious toxic effects are not common.

Administration and Dosage.—The drug is given to adults in doses of from 0.25 to 1 Gm. (4-15 gr.) in the form of pills, cachets, or water solution, 3 times daily. The course of treatment requires from seven to fourteen days. Combined oral and rectal administration has been used in acute and chronic cases. In view of the iodine content, its use in thyroid disturbance should be considered. It should be used with caution in cases of liver damage.

Vioform, N. F.—Vioform is also an oxyquinoline derivative. It is a grayish yellow powder, almost insoluble in water. It is used internally against amoebiasis and as a substitute for iodoform. From experimental results, also from results obtained in the treatment of human amoebiasis, this drug seems to be superior to chiniofon. The majority of cases treated are rendered parasite-free, and very few untoward symptoms have been observed.

Dosage.—Against amoebiasis, 0.75 to 1.0 Gm. (10-15 gr.) daily in divided doses of 0.25 Gm. (4 gr.) by mouth for ten days. After ten days' rest, the treatment may be repeated. A few cases of gastrointestinal irritation with this dosage have been reported. Iodism should be kept in mind, as also its use when goiter is present.

Diiodo-Oxyquinoline (Diodoquin), N. N. R., is used in the treatment of amoebic dysentery and in *Trichomonas* infections of the intestine. It is an iodine compound and is given by mouth in doses of seven to ten tablets a day for fifteen to twenty days. It is given between meals preferably. Its relative insolubility minimizes intestinal irritation and permits its use over a period of time. It is useful in the treatment of carriers of the amoebic organism as well as for patients with acute symptoms of the disease.

Questions for Review

1. What organs make up the alimentary tract?
2. Explain how flavoring agents may promote the desirable action of a drug
3. Why is it impossible to use as a tooth powder or dentifrice a substance which is capable of marked power of disinfection? What is the most we may expect of a dentifrice?
4. When using a salt solution for a gargle, why is it preferable to use a normal salt solution rather than a strong salt solution?
5. In what ways may drugs act upon the stomach?
6. Name several simple emetics.
7. Why should you have an emesis basin at hand when you are ready to administer apomorphine hypodermically?
8. Name several preparations which are useful to check vomiting.
9. List four common causes of constipation.
10. Name several conditions in which cathartics are contraindicated.
11. When a person walks into a drugstore and asks for a cathartic, why is a good druggist likely to inquire whether the person has any nausea or abdominal pain?
12. What are three ways by which cathartics may act upon the intestine?
13. Indicate the method of action for each of the following:
 - a. Petrolagar.....
 - b. Mineral Oil.....
 - c. Castor Oil.....
 - d. Compound Cathartic Pills.....
 - e. Cascara.....
 - f. Magnesium Citrate.....
 - g. Pituitrin.....
14. How does a laxative differ from a purgative?
15. What group of cathartics are particularly indicated for patients with edema?
16. In case of food poisoning, why would castor oil be a more suitable cathartic than cascara?
17. What type of cathartic is usually ordered for the patient with chronic constipation? Why?
18. What special care must be taken of rubber sheets when bed patients are given mineral oil? What advantage does a mixture of agar-agar and mineral oil have over mineral oil alone?
19. What "specific" drugs may be given for the treatment of tapeworms: round-worm; hookworm; pinworm?

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UNIT V

CHAPTER XIV

PHARMACOLOGY AS RELATED TO THE CIRCULATORY SYSTEM

I. ANATOMY AND PHYSIOLOGY OF THE HEART

(Points of Review)

The heart is a complex muscular pump of remarkable efficiency.

It has four chambers with a complete septum between the two sides. The efficiency of it depends on accurate timing and sequence of contraction of the ventricles in relation to the auricles. Being highly specialized, with thick muscular walls in the mammal, it requires a circulation of its own for nutrition and oxygen supply. This is furnished by the coronary circulation.

Special Tissues of the Heart.—These include (1) the sinoauricular node; (2) the functional tissue between the auricles and ventricles, including the auriculoventricular node; (3) the auriculoventricular bundle or bundle of His; and (4) the right and left septal divisions of the bundle and their branches.

The efficiency of the heart as a pump is a matter of great importance in both health and disease. Muscular work that lasts more than a few seconds demands renewed circulation. The brain deprived of circulation for a few minutes is damaged permanently. The heart itself fails almost instantly if the coronary supply is shut off. Both the timing of the auricles and the coronary circulation are frequently damaged by disease.

Heart muscles resemble other muscles in the possession of three qualities: tone or maintained mild contraction; irritability or readiness to respond to stimulation; and contractility. The contractility of heart muscles differs from that of other muscles in that it is rhythmic and that it depends upon certain intrinsic properties of the muscle itself and not alone upon impulses received through nerves. Moreover, the auricles and ventricles of the heart can contract independently of one another; the auricles are capable of beating three times as fast as the ventricles whose intrinsic rate is 30 to 40 beats per minute. The contraction wave begins in the

auricles and is transmitted by the auriculoventricular bundle to the ventricles, which pump the blood into the arteries and determine the pulse. Normally the beat of its auricles is followed in about a fifth of a second by the beat of the ventricles, the whole contraction forming the systole which occurs about 72 times a minute. Each systole or contraction is followed immediately by a period of relaxation called the diastole.

Heart muscle differs from skeletal muscle in that its refractory period is relatively long. This means that heart muscle will not respond to a second stimulus as long as its fibers are in a contracted state.

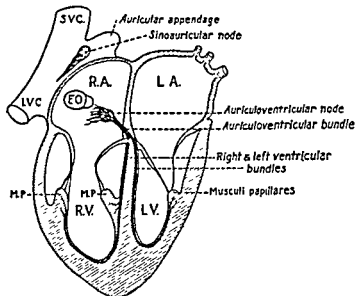


Fig. 13.—Diagram to show the general ramifications of the conducting tissue in the heart of the mammal. It will be observed that there is none of this tissue between the sino-auricular and auriculoventricular nodes. (From Bard; *Macleod's Physiology in Modern Medicine*.)

The long refractory periods of cardiac muscle help to preserve the cardiac rhythm. Although the muscle is only relatively refractory during diastole, response to further stimulation is discouraged until complete relaxation of the muscle fibers has occurred.

Blood Supply of the Heart.—The blood which flows through the heart nourishes only the cells of the endocardium. The pericardial arteries supply the pericardium while the right and left coronary arteries are the important sources of blood for the heart muscle itself. The flow of blood through the coronary arteries is greatest during diastole and least during systole although the coronary outflow is greatest during ventricular systole. Consequently prolonged rapid heart action is prone to result in a poorly nourished and hence

a weakened heart muscle. The coronary vessels are supplied with nerve fibers from both divisions of the autonomic nervous system.

Nerve Supply of the Heart.—The contractions of the heart muscle are regulated by the accelerator nerves of the sympathetic nervous system and by the inhibitory nerves, the vagi of the parasympathetic division. Stimulation of the accelerator nerves causes the heart to beat stronger and faster. The impulses originate in the cardio-accelerator center of the medulla, pass over the nerves and activate the sinoauricular node or the pacemaker of the heart. The periods of rest and diastole are therefore shortened. Stimulation of the inhibitory nerves causes the heart to beat more slowly and weakly. The period of relaxation or diastole is longer. Activation of the vagus nerve may result from stimulation of the vagus center in the medulla or anywhere along the course of the nerve or in the endings and myoneural junctions. The vagus is the only nerve, stimulation of which directly slows the heart. High blood pressure from any cause tends to slow the heart by reflex stimulation of the vagus center in the medulla.

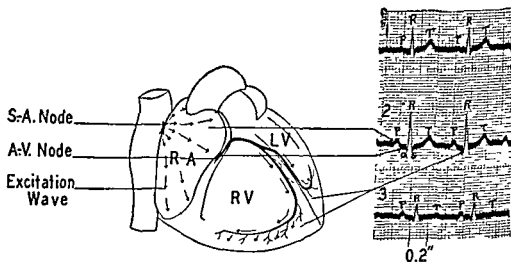


Fig. 20 —Electrocardiogram. Leads I, II, and III, with diagram of the heart showing schematically the origin of the waves. (From Bard: *Macleod's Physiology in Modern Medicine*.)

Blood Pressure.—In order that the circulation of blood through the body be continuous, it is essential that the blood exert a certain force against the walls of the vessels in which it is contained. This force is measured by changes in blood pressure. Blood pressure is modified by:

1. The rate and force of the heartbeat. A forceful heartbeat tends to raise blood pressure, whereas a weak beat tends to lower blood pressure.

2. The resistance which the blood vessels offer to the passage of blood. Vasoconstriction tends to increase blood pressure while vasodilation lowers blood pressure.

II. HEART DISEASE

Heart disease as a cause of death has assumed greater and greater proportions until now it is the leading cause of death. About one out of every six or seven deaths has been reported to be of cardiac origin.*

Congestive Heart Failure.—The symptoms of cardiac insufficiency of which a patient is likely to complain, are due to the inability of the heart muscle to function efficiently as a pump. If blood is not forced out of the heart, it will be dammed back into the big veins and into the organs drained by these veins. If the left ventricle fails, the lungs become congested and symptoms of dyspnea and cough appear. Failure of the right ventricle causes congestion in the systemic veins giving rise to generalized edema. Inefficiency in both ventricles will cause inadequate oxygenation of blood and cyanosis. Either the right or the left ventricle may fail, and usually there are manifestations of failure in both.

Coronary Disease.—When the coronary arteries become thrombosed, narrowed, or sclerosed, certain portions of heart muscle will receive an insufficient supply of blood. This will give rise to pain in the heart or heart region. Pain due to narrowing of the coronary arteries is called *angina pectoris*.

Auricular Fibrillation.—A type of arrhythmia in which a region of auricular structure transmits nerve impulses with such extreme rapidity that only portions of the auricular wall are able to respond. As a result the atrial walls quiver or "fibrillate." Likewise all of the impulses are not transmitted to the walls of the ventricles causing them to beat rapidly but irregularly and at a slower rate than the auricles. This condition is serious because the rapid rate of contraction may cause the heart to fail.

Auricular Flutter.—A form of arrhythmia very similar to auricular fibrillation except that the rate of contraction of the auricles is not as extreme. They respond to each impulse, however, so that the rate of contraction is very fast. All of the impulses are not conducted to the ventricles, but they may respond to every second or third beat with more or less regularity.

Heart Block.—Impairment of the conduction mechanism between the auricles and the ventricles may result in some impulses getting

*White, Paul D.: Heart Disease, New York, 1939 The Macmillan Company, p. 172.

through and some failing to get through. This is known as *partial heart block*. When no impulses get through, *complete heart block* is said to be present. The ventricles then beat according to a rhythm of their own and independently from the auricles although more slowly.

III. PHARMACOLOGY OF THE HEART

The drugs which are used for their effects upon the heart may be divided, for purposes of classification, into three groups:

1. The stimulants, which increase the activity of the heart and quicken the pulse.
2. The tonics, which strengthen the contraction of the heart muscle and improve the quality of the pulse.
3. The depressants, which lessen the activity of the heart and slow the pulse.

Drugs may change the rate, the force, and the rhythm of the heart.

1. Heart Stimulants

Many of these drugs have been discussed in greater detail elsewhere and will be only mentioned here.

Atropine.—Atropine makes the heartbeat stronger and faster because of its action which causes the nerve impulses along the vagi to be ineffective. Since the inhibitory action of the vagus is removed, the heart beats faster and stronger.

Caffeine.—Caffeine stimulates the myocardium directly and produces a rapid, strong pulse for a short time. It is used in treatment of collapse, or heart failure to improve breathing and pulse. Other members of the caffeine group are particularly valuable to relax coronary blood vessels in attacks of coronary disease.

Epinephrine.—Epinephrine may be given intravenously or intramuscularly as a powerful emergency circulatory stimulant. When given intravenously it must be well diluted, given slowly, and in small quantities. Its effects appear to be due chiefly to its power as a vasoconstrictor although some authorities maintain that it stimulates the myocardium directly and also the conduction tissue.*

Metrazol, Coramine, and Camphor, through their action on the medullary centers, may act as cardiac stimulants, causing the pulse to be slower and stronger.

*Goodman and Gilman, *Pharmacological Basis of Therapeutics*, New York, 1941. The Macmillan Co. p. 403.

2. Heart Tonics

CARDIAC GLUCOSIDES

Glucosides are substances which on hydrolysis yield glucose or a related monosaccharide, and another substance. The nonsugar part is termed the aglucone or genin. In many cases the composition of the aglucone is unknown; it may be an alcohol, aldehyde, acid, phenol, etc.; usually it is an aromatic body. The sugar may be rhamnose, galactose, ribose, arabinose, or any disaccharide that yields a sugar related to glucose.

The splitting of sugar from the glucoside molecule apparently causes a decline in potency as each aglycone is less powerful on the heart than the parent glucoside molecule. The aglycones also exert a greater emetic action than the parent glucoside.

THE DIGITALIS SERIES

Many substances, of which digitalis is the most important, are characterized by their action on the heart. These substances belong to many different botanical families. For ages they have been used empirically in therapeutics. The action of each is fundamentally the same, so that the description for digitalis, with minor differences, will apply to all.

The most important plants which contain digitaloid substances are:

<i>Digitalis lanata</i>	White foxglove
<i>Digitalis purpurea</i>	Purple foxglove
<i>Strophanthus hispidus</i> <i>S. kombé</i>	(An African arrow poison)
<i>Scilla maritima</i>	Squills or Sea Onion

DIGITALIS

A. Source.—Digitalis is the dried leaves of *Digitalis purpurea* or purple foxglove. This plant is cultivated for the drug market in England, America, and Germany, and grows wild in Europe, the United States, and Australia. Early investigators gave the plant the name of "*Digitalis purpurea*" because the flower is purple and resembles a finger. Digitalis leaves contain a number of glucosidal active principles, the most important being digitoxin, gitalin, and digitalin.

B. Local Action.—Local irritation is marked. If a small quantity of digitalis be placed in the eye, intense pain, redness and congestion of the conjunctiva, and all the symptoms of inflammation follow. When a solution is held in the mouth, it is frequently followed by burning pain. When swallowed, the local irritation of the stom.

ach may cause vomiting. If drawn into the nostrils, it elicits sneezing, coughing, and hoarseness, and in a good many persons marked swelling of the mucous membranes. When injected hypodermically, it produces pain and sometimes abscess formation which forbids this method of administration. Intramuscular injections are sometimes used although they are not painless and not advisable, since in many cases abscess follows. Digitoxin is a more powerful irritant than digitalcin, which may be injected subcutaneously almost without pain.

C. Cardiovascular Action.—The total result of action on the heart is a stronger beat and sometimes a slower rate. These effects are brought about by an action on several mechanisms and experimental analyses of these are made by studying the isolated heart, a heart in situ, and isolated parts of heart muscle.

1. *Digitalis stimulates the heart muscle, causing an increased force of systolic contraction, improved tone, and increased irritability of the heart muscle.* This is apparently the most important action of the drug. The increased force of contraction in the failing heart causes the ventricles to empty more completely and allows the heart to receive an increased amount of venous blood thus relieving increased venous pressure associated with the failing heart. Increased power of contraction also promotes coronary circulation which favors recuperation of the myocardium.

2. *Digitalis brings about stimulation of the vagus mechanism whereby an increased number of inhibitory impulses is sent to the heart and to the bundle of His.* Although this action tends to result in a slower heartbeat, the present concept of the action of digitalis minimizes the slowing effect as a beneficial factor as compared to the value of increased power of muscle contraction. Improvement of symptoms of congestive heart failure in man has been noted without apparent slowing of the cardiac rate. Slowed heart action and partial heart block are often seen, however, particularly after the administration of large doses.

D. Expected Result of Action of Digitalis.—The therapeutic action of digitalis is of course quite different from the physiologic one. The beneficial effects from this drug are to be seen particularly in the patient with congestive heart failure and may include the following:

1. *In the Body as a Whole.*—The heart beats stronger and more forcibly, resulting in improved circulation to all organs including the heart itself. From the lungs disappearance of edema makes breathing easier, from the abdomen there is relief of ascites, and



PLATE XI.—*Digitalis purpurea* (Foxglove). (From Jackson *Experimental Pharmacology and Materia Medica*.)

from all tissues of the body there is relief of the water-logged condition which may be present. Improved circulation means that more oxygen is brought to the tissues and cyanosis disappears.

2. *In the Kidneys.*—Digitalis is not a diuretic in the sense that it acts primarily on kidney tissue, but marked diuresis may be observed in patients with edema because of the improved heart action and better general circulation. The edema which forms because of venous congestion will be eliminated through the kidney.

3. *In the Blood Vessels.*—In the patient with heart failure the blood pressure may be raised or lowered or not affected at all. Therapeutic amounts of digitalis produce no significant changes in blood pressure of normal human beings.

E. Absorption, Excretion and Administration.—Digitalis when given by mouth is readily absorbed from the intestine, but not from the stomach. Local irritation of gastric mucosa is decreased by giving the drug with meals or just after meals. Some cardiac effects may be noted within six hours after the drug is given orally although twelve to eighteen hours are required in some cases. Digitalis is excreted slowly from the body. Repeated doses produce cumulative effects seen in the symptoms of poisoning. Digitalis is usually given orally although several proprietary preparations of digitalis principles are given by hypodermic for rapid effects. Intravenous administration in emergency conditions is accompanied by danger and must be done very slowly and cautiously. If patients are unable to take digitalis by mouth, rectal injections of a diluted tincture or digitalis suppositories may be given.

F. Symptoms of Overdosage and Treatment.—

1. Nausea and vomiting are among the earliest symptoms of poisoning. The nausea and vomiting which follows customary doses of digitalis is due to a systemic action and represents a toxic symptom. The severity of the symptoms depend upon the general condition of the patient, dosage, and length of time the drug has been given. These symptoms alone, however, do not indicate overdigitalization.

2. Diarrhea and abdominal pain.

3. Slow pulse, rate usually below sixty, irregularity in rate and rhythm or a sudden change in the pulse.

4. Headache, malaise, drowsiness, hallucinations, and sometimes blurred vision.

The treatment is to stop the drug and promote elimination if necessary. The patient should be kept absolutely quiet until decided improvement is seen. Atropine and ...

given to check vomiting and relieve the pain in the abdomen. Bromides and barbiturates may also be employed as sedatives.

Since toxic effects are most commonly detected by study of the action of the pulse and heart, a patient who is receiving digitalis should be under strict medical observation.

G. Therapeutic Uses.—Although digitalis is a cardiac tonic of highest rank, it does not cure heart disease. It may, however, make it much easier for the patient to live within the physiologic limits of his heart action. It is particularly valuable to—

1. Relieve the symptoms of congestive heart failure and to help prevent the recurrence of heart failure.

2. To treat auricular fibrillation and auricular flutter when associated with heart failure.

CONTRAINDICATIONS.—Digitalis is contraindicated in severe myocarditis, partial heart block, and in some cases of arteriosclerosis. Valvular disease, pneumonia, diphtheria, and thyrotoxicosis are not in themselves considered indications for digitalis therapy.

H. Standardization of Digitalis Preparations.—The U. S. P. Digitalis Unit is the result of an assay by the cat method in which an improved method of bioassay is used. One U. S. P. Unit represents the potency of 0.1 Gm. of the U. S. P. Digitalis Reference Standard (U. S. P. XIII).

I. Preparations and Dosage.—In the treatment of heart failure the aim is to give digitalis until the physiologic limit is reached, that is, until the patient has been digitalized. This may be done by giving relatively large doses until mild toxic symptoms are produced. The patient may, however, be digitalized by either a rapid or a cumulative method. The rapid method should be used only when the patient can be carefully watched and when frequent electrocardiogram studies can be made. Powdered leaf and tincture of digitalis are the preparations most commonly used for digitalization. The present method of rapid digitalization is a modification of the original Eggleston method. It has been estimated that the amount needed to digitalize an adult (who has received no digitalis for ten days) in 36 to 48 hours is 15 Gm. U. S. P. XII of the leaf and 15 cc. U. S. P. XII of the tincture. The method of digitalization depends greatly on the condition of the patient. The total dosage may be divided into equal parts and given every four or six hours or one-half to one-third of the total may be given as an initial dose and the remainder divided into two portions and given in subsequent doses four to six hours apart.

When it seems inadvisable to administer large doses of digitalis at a time, the drug is given in smaller doses several times daily until digitalization occurs.

Many patients continue to need digitalis for the remainder of their lives. In order to maintain the beneficial effects of the original digitalization a *maintenance dose* is determined to replace the drug which is daily lost or destroyed in the body tissues. Most patients require about 1 cc. U. S. P. XII of the tincture or 0.1 Gm. U. S. P. XII of the powdered leaf once or twice daily.

Preparations.—

Powdered Digitalis (*Digitalis Pulverata*), U. S. P. Dose: 0.1 Gm. ($1\frac{1}{2}$ grains). Marketed in tablets, capsules, or suppository form.

Tincture of Digitalis (*Tinctura Digitalis*), U. S. P. This is the only acceptable form of liquid preparation; 1 cc. is equal to 1.0 U. S. P. Digitalis Unit. Dose: 1 cc. (15 minims).

Digitalis Injection (*Injectio Digitalis*), U. S. P. Dose: Intravenous, 1 U. S. P. unit.

Infusion of Digitalis (*Infusum Digitalis*), N. F. The infusion is less stable than other liquid official preparations. Dose: 6 cc. ($1\frac{1}{2}$ drams).

Digitoxin, U. S. P. Digitoxin is the chief active glycoside of *digitalis purpurea*. It is available in crystalline form and is readily absorbed from the intestinal tract. One milligram of digitoxin has the same effect as 1 Gm. of U. S. P. digitalis when given by mouth. It is available in tablet form as well as in ampules. It is extremely poisonous. Average oral dose: 0.1 mg. ($\frac{1}{600}$ gr.).

Digitanid, N. N. R.; a mixture of glucosides from the leaves of the *Digitalis lanata*. Action and uses are similar to those of U. S. P. digitalis. Average dose: Liquid, 1 to 2 U. S. P. units until digitalized.

Digalen, N. N. R. Contains cardioactive principles of digitalis. Tablets for oral use, ampules for injection. Dose: $\frac{1}{2}$ to 1 cat unit three times daily.

Digifolin, N. N. R. Preparation containing the therapeutically desirable constituents of digitalis leaf. Tablets for oral use, ampules for injection. Dose: oral, 0.8 U. S. P. unit four times daily until desired effects are obtained.

ESSENTIALS IN NURSING CARE

Patients who have heart conditions which demand digitalis therapy usually require rest in bed and such anticipation of their needs

as will cause them to expend a minimum of energy. An upright position in bed with adequate support will help to relieve dyspnea and a table made high and wide enough to slip over the bed on which the patient can lean will afford change of position and greater comfort. Sometimes patients are much distressed if they are kept in bed and in such instances it may be better to make them comfortable in a suitable chair. Other things expected of the nurse would include—

1. Careful measurement and record of intake and output of fluids
2. Observation of the patient's color, degree of edema, and dyspnea
3. Prompt and accurate administration of the drug with attention to symptoms and signs of early toxicity, especially as related to changes of the pulse. The pulse should be counted prior to giving each dose and if it has slowed to a count below 60 beats per minute or if there is a sudden change in the beat, the drug should be withheld and the doctor notified.
4. Careful record of the patient's weight.

OTHER DRUGS OF THE DIGITALIS GROUP

Digilanid, N. N. R., is a mixture of several glucosides obtained from the white foxglove, *Digitalis lanata*. They are known as Lanatoside A, Lanatoside B, and Lanatoside C. The action of digilanid is very similar to that of digitalis U. S. P.

Digoxin, U. S. P. (Cedilanid-Sandoz). There is reason to believe that Lanatoside C (Digoxin) is of greater therapeutic value than the other two glucosides of *Digitalis lanata*. Digoxin is formed from Lanatoside C. It has an advantage over digitalis for the patient who must be rapidly digitalized. Some patients seem to tolerate Digoxin better than digitalis. The drug may be given intravenously in which case saturation of the tissues may be accomplished much more rapidly than with digitalis. Digoxin may also be given orally. It should be administered with caution because it is extremely poisonous. It may bring about digitalization within a few hours when it is administered by mouth and within a few minutes when given intravenously. The average dose when given by mouth is 0.5 mg. ($\frac{1}{120}$ grain) and when given intravenously the dosage must be determined in terms of the needs of the patient, although 0.75 to 1.0 mg. may be given as an initial dose for rapid digitalization. For maintenance 0.25 mg to 0.75 mg. by mouth and 0.25-0.5 mg. intravenously may be given. Digoxin is a tissue irritant and the contents of the ampul should be diluted before giving.*

*N. N. R., 1947, p. 251.

Strophanthin, N. F., is practically identical in action with digitalis. It is not easily absorbed from the gastrointestinal tract and hence is not satisfactory to give by mouth. When given by intravenous or intramuscular injection, it acts promptly and efficiently, and its use is indicated when immediate action is advisable. The dose of strophanthin is 0.5 mg. ($\frac{1}{120}$ grain) by hypodermic injection, a single dose only being given daily.

Strophanthin should be used with special care if the patient has had a full course of digitalis within the preceding three weeks. Strophanthin and the glucosides of digitalis are the most important glucosides used in medicine.

Ouabain, U. S. P., or G-Strophanthin, is a crystallized strophanthin of definite composition obtained from *Strophanthus Gratus* (hence the G). Owing to its definite composition, it is a reliable standard. It is more active than the official Strophanthin when injected intramuscularly or intravenously. It is, however, quickly excreted and has less cumulative action than digitalis.

Oral administration of the drug is not recommended because of the uncertainty of absorption. The dose for intramuscular or intravenous injection is 0.5 mg. which should not be repeated in less than twenty-four hours unless the dose is decreased.

Scillaren, N. N. R.—Scillaren and Scillaren-B are mixtures of natural glucosides of the same proportions as found in the squill or sea onion (*Urginea maritima*). The action of this drug on the heart is similar to that of digitalis but less persistent. It is given as a Syrup of Squill, N. F., 2 c.c. or in the form of Scillaren, $\frac{1}{40}$ grain two to three times daily, or Scillaren-B, $\frac{1}{120}$ gr. The latter is used for intravenous injection and is not to be repeated within twenty-four hours.

Squill may also be used as an expectorant, emetic, or diuretic, but it is usually associated with other agents when prescribed for these uses.

3. Heart Depressants

Heart depressants are drugs which lessen the action of the heart and slow the pulse by depressing the cardiac muscle or by stimulating the vagus nerve. Their use is indicated when the heart is overirritated or inflamed. The drug most commonly used for this purpose at the present time is *quinidine sulfate*.

Quinidine Sulfate, U. S. P., is the sulfate of the alkaloid quinidine, obtained like quinine from cinchona bark. It acts directly on muscle of the auricles, decreasing its irritability and rate of conduc-

tivity. It slows the heart and lengthens the time of conduction between the auricles and ventricles by increasing the refractory period in the sinoauricular node and auricular muscle. It thus changes a rapid irregular pulse to a slow regular one. The Amplitude of contraction may be increased in the compensated heart thus causing increased filling of the ventricles. Toxic doses, however, decrease the Amplitude of contraction. Quinidine is a depressant while digitalis and strophanthin are stimulants or tonics.

Quinidine sulfate is used to check auricular fibrillation and restore the normal rhythm of the heart. It is most successful in the treatment of cases of fibrillation of short duration or of a paroxysmal type. It is least useful where there is marked cardiac insufficiency.

Comparison of Quinidine and Digitalis Effects.—

1. Digitalis increases cardiac irritability while quinidine decreases it.

2. Quinidine rests the heart by depressing the abnormal pacemakers while Digitalis prevents the nagging impulses from reaching the ventricle as often.

Administration.—Quinidine sulfate is given by mouth in doses of 0.2 to 0.4 Gm. (3 to 6 grains) repeated every four hours, for from one to three days. As a rule, its effects are established within that time, and may last several months. —

Poisoning.—Quinidine may cause the following toxic symptoms: headache, flushing, nausea, vomiting, fainting, palpitation, and convulsions. Cases of sudden failure of respiration have been reported from comparatively small doses. Idiosyncrasy is not uncommon.

Successful treatment with quinidine depends on careful selection of cases and proper dosage of the drug. It is contraindicated in patients with quinine idiosyncrasy, acute infection, marked cardiac damage, or in patients with marked hyperthyroidism.

IV. PHARMACOLOGY AS RELATED TO THE BLOOD VESSELS

A. The Coronary Blood Vessels

Much confusion exists regarding the reactions of the coronary vessels to drugs and products of metabolic origin. The reason for this confusion is the complexity of the physiology involved. Besides a direct action on the coronary vessels, drugs may change the work of the heart and invoke secondary changes in the coronary vascular system. Hence, the effect produced on the isolated heart, or on

excised rings of coronary arteries, on which much experimental work has been done, may not be the same as on the heart of the intact animal. Epinephrine, for example, usually dilates the coronary vessels, and for this reason should be of value in some cases of coronary disease. At the same time, however, by raising the blood pressure, it increases the work of the heart to such an extent that it may do harm.

To estimate the value of a drug in increasing the coronary circulation, we must know:

1. The changes it produces in the coronary vessels.
2. The effect on the volume of coronary flow.
3. The effect on the work and energy expenditure of the heart.

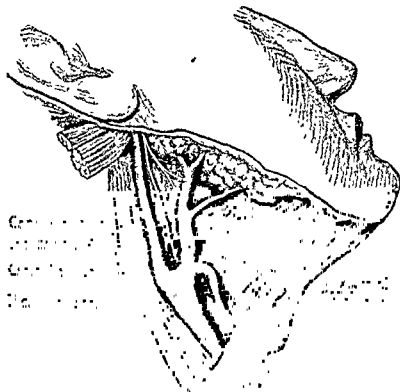


Fig. 21.—Dissection showing the position and relations of the carotid sinus and nerve in man. Pressure applied over the carotid sinus in man may slow or temporarily stop the heartbeat. (After C. Heymans.)

If a drug increases the coronary flow and at the same time increases the work of the heart more than the increased flow will compensate, it does harm. Again, the volume of coronary sinus drainage is not a true index of coronary vasoconstriction or vasodilatation. In addition to the coronary drainage, that of the Thebesian veins, which empty directly into the heart cavities, cannot be measured.

Volume of Blood Flow Through the Coronaries.—Experiments indicate that about 5 per cent of the total output of the heart flows through the coronary system. The maximum amount in experimental animals may rise to 20 per cent of the total output. The output of the human heart under basal conditions is between 3 and 4.6 liters per minute, but during strenuous exercise it may rise to 37 liters. In such a condition, if 5 per cent were to flow through the coronaries, it would equal almost 2 liters per minute. This increase under strain would explain why *angina pectoris* may develop more readily under such conditions.

There is a considerable factor of safety in the coronary circulation. Mann, Herrick et al.* found that a carotid artery may be constricted to 70 per cent of its natural lumen without affecting its volume flow. The same may be true of the coronary arteries.

THE CAROTID SINUS

The common carotid artery divides into external and internal branches. On the internal branch near the point of its branching is a dilation known as the *sinus caroticus*. It is surrounded by a rich nerve plexus, with afferent fibers which form a small nerve, the *sinus nerve*, which joins the glossopharyngeal, except for a few fibers which join the vagosympathetic trunk.

Mechanical or electrical stimulation of the carotid region stimulates the vagus reflexly and causes a slowing of the pulse (Marey's law). If the vagus nerve be cut, there is no change in the heart rate but a reflex fall of blood pressure through reflex vasodilation by an action presumably on the vasodilator center.

B. Systemic Arteries and Veins

1. Action of Drugs on Arteries.—The arteries may be contracted or dilated.

Contraction: The elasticity of the vessel wall is essential to the maintenance of the diastolic pressure. The elasticity may be lessened in arteriosclerosis. Intoxication by alcohol and lead are said to cause arteriosclerosis, but the mode of their action is not clear and in some cases (alcohol) doubtful. The toxins of acute infections and of disturbed metabolism may produce degenerative changes in the media and adventitia. Fatty degenerative atrophy and calcification may occur in the muscularis and adventitia of the involved vessels. Lime salts may be deposited in tracheal ringlike formations.

The causes of arteriosclerosis produced by drugs and toxins, seem to be due first to slow damage to the vessels, followed by calcifica-

*Surgery 4: 249, 1938.

tion and other changes. It is only by prolonged action that such changes occur.

Nicotine (smoking) is said to produce arterial changes, especially in the coronary, cerebral and arteries of the leg. Thromboangiitis obliterans is usually a disease of heavy smokers. General arteriosclerosis, however, is not more common in smokers.

Ergotism.—Ergotoxine (Ergonovine) raises the blood pressure by stimulation of the myoneural junctions of the vasoconstrictor nerves. Large doses paralyze these endings. In ergotism (gangrene form) the arterioles are contracted and filled with a hyaline-like substance.

Ergot, as is well known, when its use is long continued, or when food like rye containing ergot is eaten, may produce gangrene by contraction of the vessels and a deposit of hyaline-like material in the lumen of the vessels.

2. Action of Drugs on Veins.—The return of blood to the right heart is due in part to the *vis a tergo* which still remains after the blood has traversed the arteries, capillaries and venules, in part to the muscular pressure on the veins, and in part to the suction or negative pressure in the right heart, and in part by the contraction of the larger veins. Hooker and Donegan have presented evidence that the veins are to some extent under nervous control.

As a whole, drugs affect veins relatively little. Histamine, however, dilates the capillaries.

Varicose Veins.—Various substances such as sodium salicylate, sodium chloride, dextrose, quinine dihydrochloride, urethane, and metaphen have been injected to produce thrombosis. These substances act on the intima and provoke a coagulation thrombosis. A solution containing 13 per cent quinine and 6 per cent urethane has been found effective. Other agents used are 20 to 30 per cent sodium chloride, 40 per cent sodium salicylate, or 5 per cent sodium morhuate. Their use requires training in the technique.

VASOCONSTRICTORS

Vasoconstrictors (see Autonomic Nervous System) are drugs which constrict the blood vessels by contracting the muscle fibers in their walls or by stimulating the vasomotor center in the medulla. They thus stop hemorrhage, raise blood pressure, and increase the force of the heart. The most important vasoconstrictors are epinephrine, or adrenalin, as it is most widely known, ephedrine and pituitary extract. Epinephrine and ephedrine are discussed in detail in Chapter XIII and will be only reviewed here, in their capacity as vasoconstrictors.

Epinephrine (Adrenalin), U. S. P., is the active principle of a secretion which is normally poured into the blood stream from the medulla of the suprarenal gland. *The most important action is its powerful constriction of the peripheral blood vessels.* When applied to an abraded surface or mucous membrane, it contracts the small vessels and stops bleeding. The contraction of the blood vessels causes a prompt rise of blood pressure, which is of short duration, lasting usually not more than five minutes. The increase in blood pressure slows the heart, and causes a slow strong pulse.

The chief therapeutic use of epinephrine is to constrict peripheral blood vessels by local application. In this way it is used to diminish hyperemia of the conjunctiva, to reduce swelling of the turbinated bodies, to arrest hemorrhage from the mucosa of the upper respiratory tract, and in operations on the eye, nose or ear. It is used in bleeding from capillaries or small arteries, but it does not stop hemorrhage from a large vessel. For the arrest of hemorrhage, it must be applied directly to the bleeding vessels or congested area. It should not be given for internal, concealed hemorrhage, in which a rise in the blood pressure is not desirable.

For hypodermic or intramuscular injection 0.5 cc. (7 minims) or less of a 1 in 1000 solution of epinephrine hydrochloride in physiologic salt solution is used; for intravenous injection 0.1 cc. (1½ minims) of a similar solution is employed. It must be injected very slowly.

Ephedrine, U. S. P. (Ephedrine Base), is the alkaloid of the Chinese plant ma huang.

Ephedrine affects structures supplied by the sympathetic nervous system much like adrenalin. In small doses it raises the blood pressure and in large doses lowers it; it causes a rise in blood pressure and strengthens the heart action by contracting the blood vessels. Applied locally, it contracts the capillaries to some extent and thus reduces swelling of the turbinate bodies and lessens hyperemia.

For local application to mucous membranes, ephedrine is used in the form of the base, 1 per cent in oil, or the salts in 0.5 to 2 per cent solutions. The latter are applied as sprays.

Pituitrin is a vasoconstrictor. It acts on the arterioles and capillaries directly to cause contraction and rise of blood pressure. The rise is not as great as that produced by adrenalin but is more sustained. However, pituitrin has little clinical value as an agent to elevate blood pressure because the normal heart and blood vessel reflexes are more than able to compensate for the peripheral effects of the drug.

Ergotamine Tartrate shares with the other alkaloids of ergot the property of stimulating the smooth muscle of the uterus and the blood vessels. Ergotamine tartrate is of value in the treatment of migraine headache and has come to be considered almost a specific for this particular type of headache. Its exact mode of action is not fully understood but some authorities explain it on the basis of decreasing the amplitude of the pulsations of cranial arteries.

This drug has also been used to relieve intense itching and hives associated with jaundice, cirrhosis of the liver, or Hodgkin's disease. The dosage for migraine headache is 0.25 mg. given subcutaneously. Administration of the drug should be followed by bed rest for an hour or two. Best effects are secured if the drug is taken when the attack is just coming on. Since this drug has a cumulative action it must be used with caution. It is capable of producing all the symptoms of ergotism: numbness and tingling of the fingers and toes, muscle pains and muscle weakness, as well as gangrene and blindness.

Preparation.—

Ergotamine Tartrate (Ergotaminae Tartras), U. S. P. (Gynergen).

Average dose: 0.1 mg. ($\frac{1}{100}$ grain) orally.

VASODILATORS

Vasodilators are drugs which dilate the blood vessels by relaxing the muscle fibers in their walls or by depression of the vasomotor center in the medulla. They thus cause a fall of the blood pressure.

The Nitrites.—The *nitrite* group of drugs comprises salts of nitrous acid and certain nitrates all of which are reduced to nitrites in the body. Their characteristic action is vasodilation, due to the nitrite radical which is common to them all, and which causes muscle fibers to relax. This increases the width of the vessels, lowers the blood pressure, and relieves the heart of the overwork due to high blood pressure and to spasmodic contractions of the blood vessels. In the bronchi, they relax the spasm of muscle walls and give relief in the paroxysms of asthma. The most important members of the nitrite group are *amyl nitrite*, *glyceryl trinitrate* or *nitroglycerin*, and *sodium nitrite*. They differ chiefly in the promptness and duration of their therapeutic effects.

They are readily absorbed into the blood stream through the mucous membrane of the mouth, stomach, or lungs, inhalation being the means of administration for the volatile forms.

Epinephrine (Adrenalin), U. S. P., is the active principle of a secretion which is normally poured into the blood stream from the medulla of the suprarenal gland. *The most important action is its powerful constriction of the peripheral blood vessels.* When applied to an abraded surface or mucous membrane, it contracts the small vessels and stops bleeding. The contraction of the blood vessels causes a prompt rise of blood pressure, which is of short duration, lasting usually not more than five minutes. The increase in blood pressure slows the heart, and causes a slow strong pulse.

The chief therapeutic use of epinephrine is to constrict peripheral blood vessels by local application. In this way it is used to diminish hyperemia of the conjunctiva, to reduce swelling of the turbinated bodies, to arrest hemorrhage from the mucosa of the upper respiratory tract, and in operations on the eye, nose or ear. It is used in bleeding from capillaries or small arteries, but it does not stop hemorrhage from a large vessel. For the arrest of hemorrhage, it must be applied directly to the bleeding vessels or congested area. It should not be given for internal, concealed hemorrhage, in which a rise in the blood pressure is not desirable.

For hypodermic or intramuscular injection 0.5 cc. (7 minims) or less of a 1 in 1000 solution of epinephrine hydrochloride in physiologic salt solution is used; for intravenous injection 0.1 cc. (1½ minims) of a similar solution is employed. It must be injected very slowly.

Ephedrine, U. S. P. (Ephedrine Base), is the alkaloid of the Chinese plant ma huang.

Ephedrine affects structures supplied by the sympathetic nervous system much like adrenalin. In small doses it raises the blood pressure and in large doses lowers it; it causes a rise in blood pressure and strengthens the heart action by contracting the blood vessels. Applied locally, it contracts the capillaries to some extent and thus reduces swelling of the turbinate bodies and lessens hyperemia.

For local application to mucous membranes, ephedrine is used in the form of the base, 1 per cent in oil, or the salts in 0.5 to 2 per cent solutions. The latter are applied as sprays.

Pituitrin is a vasoconstrictor. It acts on the arterioles and capillaries directly to cause contraction and rise of blood pressure. The rise is not as great as that produced by adrenalin but is more sustained. However, pituitrin has little clinical value as an agent to elevate blood pressure because the normal heart and blood vessel reflexes are more than able to compensate for the peripheral effects of the drug.

changed by these drugs and a tolerance is easily developed. The longer acting members are the ones necessarily employed (erythrol tetranitrate and mannitol hexanitrate, $\frac{1}{2}$ -1 grain tablets every four to six hours).

Symptoms of Poisoning.—The skin surface may become cold and cyanotic, and the patient complains of dizziness, faintness, and a throbbing headache. Unconsciousness may follow and in cases of large doses death may be due to paralysis of respiration from methemoglobin formation.

Treatment.—Place the patient in a prone position and treat for shock. Administer oxygen if the patient is cyanosed.

Preparations.—

Amyl Nitrite (Amylis Nitris), U. S. P. Dose: 0.2 cc. (3 minims) by inhalation usually.

Glyceryl Trinitrate Tablets (Tabellae Glycerylis Trinitratis), U. S. P. (Nitroglycerin Tablets). Dose: 0.4 mg. ($\frac{1}{150}$ grain) sublingually or hypodermically.

Spirit of Glyceryl Trinitrate (Spiritus Glycerylis Trinitratis), N. F. (Spirit of Nitroglycerin). Dose: 0.06 cc. (1 minim) orally. Care should be taken in handling, as it may explode if dropped on the floor, heated, or violently agitated. If any is spilled it should be covered with a solution of sodium hydroxide.

Sodium Nitrite Tablets (Tabellae Sodii Nitritis), U. S. P. Dose: 60 mg. (1 grain) orally.

Erythrityl Tetranitrate Tablets (Tabellae Erythritylis Tetranitratis) U. S. P. Dose: 30 mg. ($\frac{1}{2}$ grain) orally.

Spirit of Ethyl Nitrite (Spiritus Aethylis Nitritis) N. F. (Sweet Spirit of Niter). Dose: 2 cc. (30 minims) orally.

Papaverine.—Although papaverine is one of the alkaloids of opium, it is free of narcotic action, has a low level of toxicity, and neither tolerance nor habituation to its use has been reported. The main action of papaverine is to relax smooth muscles, especially those of the blood vessels. Relaxation occurs particularly if spasm has been present.

Good results have been obtained by the use of papaverine for peripheral or pulmonary embolism. It acts by increasing the collateral circulation in vascular beds which have been reflexly constricted. When given intravenously in doses of 20 to 100 mg., disturbance of sensation or pain may be very well relieved. It has also been used to prevent threatened gangrene in patients suffering from

Action and Result.—The nitrites act upon the smooth muscle of the blood vessels, particularly that of the smaller blood tubes. The most immediate effect to be observed is a fall in blood pressure and an increased flow of blood through the blood capillaries. Relaxation and increased blood flow through the coronary vessels is the basis for their greatest therapeutic use. Relaxation of the vessels in the skin results in a deep flush and increased skin temperature. A similar effect in the meningeal vessels results in increased intracranial pressure which in turn may be great enough to cause marked headache. Increased intraocular tension may result from dilated retinal vessels, hence the need for avoidance of nitrites in patients with glaucoma. Blood vessels in the visceral organs are also relaxed and venous return to the heart augmented.

Other types of smooth muscle which are relaxed by the nitrites are those in the bronchial tubes, the urinary system, the biliary tract, and the gastrointestinal tract. In all cases the muscle which is overcontracted or spastic is the muscle which gives most marked response.

Tolerance to the nitrite group of drugs is easily developed and necessitates the employment of the smallest dose of the drug that will give satisfactory results so that dosage may be stepped up as the tolerance increases. On the other hand, tolerance is rather easily broken and some think it advisable to alternate with some other vasodilator after a period of two or three weeks to allow the state of tolerance to be diminished.

Therapeutic Uses.—

1. **Angina Pectoris.** To relieve the pain associated with the spasm of the coronary vessels promptly, amyl nitrite is the preparation of choice. It is prepared in glass ampules (pearls) containing 3 minims of the drug and when it is needed, the ampule is crushed in a handkerchief and some of the contents inhaled. The patient should not inhale more than three times to prevent overdosage. Almost immediately the skin becomes flushed, the blood pressure falls, and the pulse and respiration are accelerated. Nitroglycerin is also used for the relief of angina pectoris. The preparation is held under the tongue. Two or three minutes elapse before its effect can be noted.

2. To relieve spasm of smooth muscle in pylorospasm, biliary or renal colic, or in bronchial asthma.

3. The nitrites have been employed in the symptomatic treatment of patients with essential hypertension. Although the blood pressure may be lowered, the underlying cause of the condition is not

changed by these drugs and a tolerance is easily developed. The longer acting members are the ones necessarily employed (erythrol tetranitrate and mannitol hexanitrate, $\frac{1}{2}$ -1 grain tablets every four to six hours).

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ergotism. It has been given in combination with codeine in conditions of nasal discharge and rhinitis (codeine sulfate, gr. $\frac{1}{4}$, and papaverine hydrochloride, gr. $\frac{1}{4}$).

It is not as effective an antispasmodic in the treatment of asthma as epinephrine or as effective as the nitrites in case of biliary spasm.

The Xanthine Group.—The xanthine derivatives, caffeine, theobromine, and theophylline, act on the nervous system, the kidneys, and the circulatory system. They are included here because of their circulatory effects. Caffeine is fully discussed under the drugs acting as central nervous system stimulants.

Both theobromine and theophylline depress the smooth muscle fibers of the blood vessels, bronchial tubes, and the biliary tract of the body. Relaxation of the muscles is particularly noticeable if the muscles have previously been in spasm. One of the most marked effects is seen in the coronary arteries.

Uses: These drugs have been used rather extensively in the treatment of angina pectoris. Their true status in the treatment of coronary arterial spasm is, however, highly controversial. The average single dose for the theophylline compounds is approximately 0.25 Gm. and 0.6 Gm. for the theobromine salts.

Alcohol.—Alcohol produces vasodilation, especially in the cutaneous vessels by a direct depression of the vasomotor center in the medulla. As a result the skin becomes warm and flushed. Alcohol is used for its vasodilating effect in the treatment of certain peripheral vascular diseases such as thrombo-angiitis obliterans, Raynaud's disease, etc. Some authorities consider moderate amounts of alcohol beneficial in the relief or prevention of attacks of angina pectoris because of its activity as a vasodilator. Whisky and soda is recommended as the alcoholic beverage of choice for cardiac patients.

Acetyl-Beta-Methylcholine (Mecholyl).—When given in adequate doses acetyl-beta-methylcholine brings about peripheral vasodilation, increased skin temperature, and reduction of blood pressure. Therapeutic results are best observed in cases where the blood vessels have been in spasm rather than where definite changes have rendered the vessel incapable of dilatation. This drug is used in selected cases for the treatment of peripheral vascular disease, varicose ulcers, and phlebitis. The drug is marketed for oral use in 200 mg. tablets. (For further discussion, see p. 229.)

Thiocyanates.—Both sodium and potassium thiocyanate were introduced into medicine for the symptomatic treatment of essential hypertension. The thiocyanate ion has two major actions in the body, one action being similar to that of the nitrites and the other like that of

the iodides. It relaxes the smooth muscles in the blood vessels in a way similar to the nitrites and it is for this effect that it is given to patients with essential hypertension.

It resembles the iodides in that it is capable of causing skin and mucous membrane reactions similar to those seen in iodism. The thiocyanates are more or less readily absorbed from the intestinal tract and are excreted mainly by the kidneys. The rate of excretion is unpredictable and hence it is necessary to determine the blood serum level of the drug in order to regulate the dosage. The safe limit is thought to be between 8 and 14 mg. per 100 cc. of blood.*

The thiocyanates are toxic and many patients exhibit some symptoms of toxicity even when they are receiving apparently safe doses. Mild symptoms include muscular weakness, fatigue, lethargy, cramping of the leg muscles, nervous irritability, and skin eruption. Enlargement of the thyroid gland may accompany prolonged therapy. Severe reactions consist of vascular collapse and more nervous manifestations—mental confusion, delirium, etc. Dosage: Potassium Thiocyanate 0.3 Gm. (5 grains); Sodium Thiocyanate 0.3 Gm. (5 grains).

Histamine.—Histamine is an amine derived from the amino acid, histidine, by the removal of the carboxyl group. It is naturally found in the intestinal content and wherever proteins are broken down by putrefactive organisms. It is also found in small amounts in ergot preparations. It has been of interest especially since it has been noted that a resemblance exists between surgical shock and histamine poisoning. As histamine is formed in the body, it appears to have no particular effect until it is released into tissue fluids as a result of certain specific stimuli.

Action.—When given orally, histamine is destroyed in the intestinal tract. After parenteral administration it produces a direct stimulation of certain smooth muscles and is a powerful vasodilator in the capillary beds. In man, a noticeable dilatation of the arterioles is also seen. Circulatory effects differ, however, in different species of animals.

The marked dilatation of the arterioles and capillaries by histamine produces a very definite flushing of the skin, rise in skin temperature, and fall in blood pressure. Vasodilation in the meningeal vessels is accompanied by an increase in intracranial pressure which may produce headache. The fall in blood pressure after small doses of histamine is followed by rather quick recovery due to the release of adrenalin and the activity of the cardiovascular reflexes.

*Goodman and Gilman, p. 573.

Uterine and intestinal muscles are stimulated as well as the smooth muscle in the bronchial tubes. Bronchial spasm may be induced in man after large doses of the drug, especially if the patient suffers from chronic conditions of the respiratory tract such as asthma, bronchitis, etc.

Histamine stimulates the gastric, salivary, pancreatic, and lacrimal glands. The chief effect in man, however, is seen in the gastric glands. The resulting secretion in the normal stomach is high in acid due to the selective action on the acid-forming cells.

Histamine Shock.—A marked fall in blood pressure may follow a large dose of histamine and the same vascular changes may occur as take place in surgical shock. The permeability of the capillary beds increases and sufficient blood proteins are lost to the tissues that blood volume cannot be maintained and circulation is slowed.

Some investigators maintain that histamine is liberated in the body in large amounts as a result of extensive tissue damage, or as a result of antigen-antibody reactions. Attempts to demonstrate that histamine tolerance can be achieved by desensitization of the patient have been inconclusive.

Symptoms of Poisoning and Treatment.—

Rapid fall in blood pressure.

Intense headache.

Dyspnea, flushing of the skin.

Vomiting, diarrhea.

Shock and collapse.

The toxic symptoms are rarely dangerous. Stimulants may be given and if shock occurs, the blood volume may need to be restored. Elevation of the foot of the bed is often sufficient treatment.

Ordinarily, histamine is rapidly destroyed in the body partly by oxidation and partly by an enzyme, histaminase. Histaminase is present in greatest amounts in the intestinal mucosa and kidney. Histaminase acts slowly to inactivate histamine. It has been reported that serum sickness, bronchial asthma, and anaphylactic disorders have responded favorably to histaminase therapy, but further study and observation of its effects in living tissues has resulted in the conclusion that it neither prevents or relieves anaphylactic reactions.

Uses.—

1. As a diagnostic agent in gastric function tests to determine whether achlorhydria is due to functional or organic causes.
2. Histamine may be used to test the capacity of capillaries to dilate in certain peripheral vascular diseases

3. It has been employed as a vasodilator in the treatment of conditions in which there is evidence of vasospasm and insufficient blood circulation. Dilute solutions may be given intravenously in this form of treatment which is still very much in an experimental stage. Claims for its therapeutic value are not well substantiated.

Preparations.—

Histamine Phosphate (Histaminae Phosphas), U. S. P. Dose: 0.3 mg. ($\frac{1}{200}$ grain) subcutaneously.

Histamine Phosphate Injection (Injectio Histaminae Phosphatis), U. S. P. Dose: 0.3 mg. ($\frac{1}{200}$ grain) intramuscularly.

Histamine-Antagonizing Agents.—

Antihistaminic Agents.—During the past few years histamine antagonists of various types have been tried for histamine shock, anaphylactic reactions, and allergy. A number of compounds have given promise of usefulness. In this country Pyribenzamine and Benadryl appear to be useful symptomatic remedies in the treatment of urticarial dermatosis, reactions to sulfonamide compounds and penicillin, atopic dermatitis, and seasonal hay fever. Their usefulness for vasomotor rhinitis and asthma is more limited. These preparations have a palliative usefulness, however, rather than an ability to immunize the patient or even protect him over a period of time against allergic reactions. In other words, their benefit is comparatively short lived and purely symptomatic. Furthermore, continued study of their untoward effects may ultimately cause their use to be abandoned.

Diphenhydramine Hydrochloride, N. N. R. (Benadryl Hydrochloride).—

Action and Uses.—Diphenhydramine Hydrochloride is antagonistic to many of the effects of histamine. Experimentally it relieves anaphylactic and histamine shock in guinea pigs and exerts an antispasmodic effect on smooth muscle.

It has been found useful in the treatment of urticaria and in the control of various allergic manifestations, although relief of symptoms is obtained only while the drug is being taken. It does not seem to be especially effective for the relief of pruritis other than the itching associated with allergic reactions.

Side reactions of drowsiness, dizziness, dryness of the mouth, nausea, and nervousness have been reported. Sedatives and hypnotics should be administered with caution to those patients receiving the drug because excessive drowsiness develops in 30 to 40 per cent of patients receiving it and may be severe enough to warrant its dis-

continuance.¹ It does not appear to have a cumulative action and can be taken over a period of time without ill effects.

Dosage.—It is recommended that the dosage be kept as low as will produce control of symptoms. The average adult dose is 50 mg. three or four times daily and lower if a smaller dosage will control the symptoms.* If relief is not obtained within the first few days, Benadryl is unlikely to be of value subsequently and administration should be discontinued.

Indiscriminate use of this drug should be avoided because of the dangers associated with some of the untoward reactions (confusion and loss of judgment). Patients should be warned about driving a car or operating potentially dangerous machinery while taking the compound.

N'Pyridil N'-Benzyl N-Dimethylethylenediamine (Pyribenzamine).—Although Pyribenzamine is neither official or included in N. N. R. it seems to be one of the most promising of the antihistamine drugs. There is evidence that it combats the hypotension and bronchial constricting effects of histamine and that it will protect a sensitized laboratory animal against anaphylactic death. Clinically it compares with Benadryl as to usefulness and side effects, although the latter are said to be of a milder order and occur less frequently than with Benadryl. Slight drowsiness is the most commonly observed side effect. An additional advantage over Benadryl is that larger doses are tolerated. It is administered orally in 50 mg. doses three or four times a day.

V. PHARMACOLOGY AS RELATED TO THE BLOOD

Significant Characteristics of the Blood.—Blood is a form of liquid tissue which consists of a straw-colored slightly alkaline fluid called plasma, and cells; red blood cells (erythrocytes), white blood cells (leucocytes and lymphocytes), and blood platelets or thrombocytes. Red cells are found to the extent of between *four and a half and five million per cubic millimeter* the number being slightly lower in women than in men. The chief constituent of the red cell is an iron and protein compound called *hemoglobin*. Hemoglobin has the important characteristic of being able to form an unstable combination with oxygen which enables it to transport that element to the tissues and give it up readily. The amount of hemoglobin in the blood should be around *15 grams per 100 cc. of blood*, again being somewhat less in women and slightly more in men. Hemoglobin is also able to form

*N. N. R., 1947, p. 20.

combinations with other substances such as drugs or certain gases, which may prevent the blood from carrying an adequate amount of oxygen to the tissues.

A deficiency in the red cells of the blood or in the total amount of hemoglobin constitutes *anemia*. An abnormal increase in red cells is called *polycythemia*.

The number of white cells is approximately 5,000-7,000 up to 10,000 per cubic millimeter. Infectious diseases may cause a marked increase which is called *leucocytosis*. Other diseases and certain drugs may deplete the normal number of white cells, in which case the deficiency is known as *leucopenia*.

The ability of the blood to clot is due to the presence of blood-clotting substances which become active as soon as the blood is released from the blood vessel. The normal coagulation time is from *three to five minutes*.

The normal reaction of blood is slightly alkaline, having a pH of 7.35 to 7.43 which is maintained with considerable constancy due to the presence of buffer substances and the power of the kidneys and lungs to excrete substances which would otherwise change the pH. The chief buffer substances are the basic phosphates, sodium carbonate, sodium bicarbonate, and the serum proteins.

Normal blood is about five times more viscous than water. The viscosity depends largely upon the presence of cells. The viscosity of the serum is about twice that of distilled water. The osmotic pressure of the blood is that of an 0.85 per cent sodium chloride solution. A solution of this concentration is said to be isotonic with the blood. Plasmolysis of cells will occur with the introduction of large amounts of hypertonic solutions into the blood while hemolysis is produced by hypotonic fluids.

Action of Drugs on the Blood.—Drugs that raise or lower the blood pressure may have little or no effect on the blood itself. A number of drugs, however, change the composition of the blood, or act on organisms in the blood.

They may be further classified as (1) blood stimulants or tonics, (2) blood depressants, (3) coagulants, (4) anticoagulants, (5) drugs which increase alkalinity, (6) drugs which decrease alkalinity.

1. Tonics or Blood Stimulants

Tonics are drugs which improve the general condition of the patient, stimulate his appetite and digestion, and make him feel stronger and more energetic. They produce these results chiefly by their effect on the blood.

Drugs may affect the blood in the following ways: either by increasing the quantity of plasma or the number of red or white cells, or both; or by improving the quality of the red blood cells by increasing their hemoglobin content.

The action of the hemoglobin is largely due to the presence of iron which is also an essential constituent of the other tissues. The normal amount of iron in the human body is 40 to 55 grains. Part of this amount is stored up as a reserve supply in the bone-making organs, liver, spleen and bone marrow, and a daily intake of $\frac{1}{10}$ to $\frac{1}{4}$ grain is necessary to keep the supply constant. This is best acquired in the form of organic iron through a diet rich in red meat, eggs, green vegetables, and whole wheat bread. However, after a severe hemorrhage, or in chronic wasting diseases such as cancer and tuberculosis, the reserve supply becomes exhausted and the hemoglobin content of blood is so greatly depleted that diet alone cannot supply the deficiency and a condition results which is known as anemia. The drugs which were commonly used in the past in the treatment of anemia were iron and arsenic; preparations of liver have been used with marked success.

Iron

Iron is a metallic element which is rather widely distributed in the body, being found not only in the hemoglobin of the blood but also in the chromatin of the cells and as a reserve supply in the blood-forming organs. Iron is essential to the normal transportation of oxygen in the body and to normal tissue respiration. Iron deficiency results in a form of anemia which is associated with symptoms of low vitality, skin and mucous membrane pallor, fatigue, poor appetite, etc.

Absorption and Excretion.—A number of different iron compounds are used in the treatment of secondary anemia. These include ferric and ferrous salts of iron, metallic iron, inorganic and organic salts. The soluble salts of iron have a more unpleasant taste, are more likely to stain the teeth, and are more likely to cause gastrointestinal disturbance than the less soluble salts. The former, however, are absorbed more readily. The hydrochloric acid of the stomach acts to change many of the ferric salts to ferrous ones and also helps to prevent formation of insoluble salts. Absorption of iron seems to occur best in the duodenum and upper part of the jejunum regardless of the type of iron administered. The old idea that only organic iron can be utilized by the body has been disproved. In fact it is believed that much more rapid response is

made by the body to the administration of inorganic than to organic preparations. The amount of absorption is dependent upon a number of factors: (1) the degree of acidity of the gastric and intestinal content, (2) the extent to which ionization of the iron salts takes place, and (3) probably the presence of bile in the intestine.

At best, the amount of iron which is permanently absorbed is small. Most of it escapes absorption and is lost in the stool or is reexcreted through the epithelium of the large bowel. The difficulty encountered in obtaining adequate permanent absorption explains the need for large doses of iron.

Body Needs for Iron.—During periods of rapid growth and development the body need for iron is correspondingly increased. Pregnancy, early adolescence (especially in girls), early childhood, and menopause constitute periods when the iron content should be increased either by increased dietary intake or medicinal iron or both. There is an increased need also when wasting diseases such as cancer or tuberculosis bring about rapid depletion of the body reserves.

The average diet for an adult American is said to contain between 10 and 20 mg. of iron per day. The normal requirement for an adult male is between 5 and 8 mg. daily. Women up through the age of menopause require from two to four times as much as the adult male. This is due to pregnancies, loss of menstrual blood, etc. While the body requirements can ordinarily be met by making provision that the diet is adequate in red meats, green vegetables, egg yolk, whole wheat, and other foods rich in iron, during periods of increased need for iron, the administration of medicinal forms may be necessary to maintain normal blood values and the balance between absorption and excretion.

Action and Result of Action.—

A. Local.—When inorganic iron compounds are administered orally, iron acts as an irritant and astringent. It reacts with tissue proteins and forms an insoluble iron compound. Extensive irritation and astringent action along the gastrointestinal tract may cause nausea and vomiting, constipation or diarrhea, and abdominal distress. Organic forms do not cause the same irritation because of the fact they dissociate with difficulty.

B. Systemic.—The action for which iron is most often administered is its hemopoietic one. If the iron reserves of the body are depleted, they are restored when ample amounts are administered. It is believed that the action of iron in conditions of deficiency is

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Mass of Ferrous Carbonate (Massa Ferri Carbonatis), N. F. Dosage: 0.6 Gm. (10 grains).

Ferric Ammonium Citrate (Ferri et Ammonii Citrates), U. S. P. This preparation contains about 17 per cent of trivalent iron. It is one of the most soluble preparations of iron. It may be dispensed in water, aromatic elixir, or in capsules. Dosage: 1 Gm. (15 grains) several times daily.

Ferrous Sulfate (Ferri Sulfas), U. S. P. This preparation has come to be one of the most widely used preparations of iron. It contains about 36 per cent bivalent iron. It is usually prescribed in tablets or pills which are coated to prevent oxidation. Dosage: 0.3 gram (5 grains) several times daily.

Syrup of Ferrous Iodide (Syrupus Ferri Iodidi), N. F. This preparation has the properties of both iron and iodine. Dosage: 1 cc. (15 minims).

Tincture of Ferric Chloride (Tinctura Ferri Chloridi), N. F. Contains about $4\frac{1}{2}$ per cent of iron. Dosage: 0.6 cc. (10 minims).

There are a number of other iron compounds listed in the United States Pharmacopoeia and National Formulary, but all the beneficial effects of iron therapy may be secured from adequate dosage of one or more of the above forms.

Copper is thought to enable the body to utilize iron better in the formation of hemoglobin, and it is frequently given with iron. Most of the preparations of iron, however, contain traces in sufficient amount.

Administration.—Inorganic preparations of iron, because they are irritant to the stomach, should be given after meals. To avoid injury or staining of the teeth, solutions should be taken through a glass tube or straw. Because of the astringent property of these preparations, they may be combined with or accompanied by some cathartic to insure regular movements of the bowels. Iron stains silver; a silver spoon should never be used in giving iron. Such stains may be removed with strong ammonia water. Iron stains on linen and clothing may be removed with oxalic acid. Since iron combines with tannin or tannic acid to make ink, iron and tea should not be given together. The oral route is by far the best route of administration. Occasionally or in rare instances iron may be given parenterally (intramuscularly) when for some reason a patient cannot tolerate the drug in the gastrointestinal tract or refuses to do so. Parenteral injection, however, is usually painful and may be dangerous.

largely to replace that which is needed for the hemoglobin molecule. The exact mechanism by which iron is utilized by the bone marrow is unknown. Iron is of value only in hypochromic anemias or those in which the color index is low. Iron therapy in this condition can be expected to result in increased vigor on the part of the patient, increased resistance to fatigue, improved condition of the skin and nails, improved appetite, and general feeling of well-being. In other words, it brings about a tonic effect. When administered to individuals with normal blood values it does not bring about an increase in the hemoglobin but only increases the reserve supply in the body.

Therapeutic Uses.—1. *Hypochromic anemia.* This is a form of iron deficient anemia such as may be seen in patients after hemorrhage. This form of anemia is markedly benefited by the administration of medicinal iron, while it is useless in the treatment of pernicious anemia. Maximum response may be expected in the case of the former between the second and fourth week. Favorable response may, however, be inhibited by vitamin deficiency, infection, achlorhydria, hepatic disorder, or disorder of absorption in the intestine. If the iron deficiency is a severe one, other forms of therapy may be needed to supplement the iron therapy. Blood transfusion will restore the blood more rapidly than anything that can be done. Other measures include adequate diet, plenty of sunshine, and the administration of hydrochloric acid if there is evidence of deficient gastric acid.

Chlorosis, an iron deficiency condition sometimes seen in young girls, responds well to iron therapy.

2. Solutions of ferric iron are sometimes used for their strong astringent properties. They are applied externally as styptics. Ferric solutions are also occasionally used as gargles for their astringent effects.

Preparations.—

Reduced Iron (Ferrum Reductum), N. F. This contains not less than 90 per cent metallic iron. It is given in the form of a powder, in capsules after meals. Dosage: 0.5-1.5 Gm. ($7\frac{1}{2}$ -22 $\frac{1}{2}$ grains).

Pills of Ferrous Carbonate (Pilulae Ferri Carbonatis), N. F. (Blaud's Pills). These pills contain iron sulfate, potassium carbonate, and sugar, with glycerin, tragacanth, and althea to make a mass. Dosage (Average): 5 pills. In severe anemia, however, it may be necessary to give 30 to 60 pills daily. The pills should be fresh.

decreased in pernicious anemia but the immature forms are increased. Arsenic inhibits the formation of leucocytes when they are excessive and this explains its use in some forms of leucemia.

6. Central Nervous System.—Chronic use of arsenic is prone to lead to the development of a peripheral neuritis.

Arsenic has been regarded as a tonic, but the tonic effect is probably the early sign of poisoning. The value of arsenic as a general tonic is very doubtful.

Symptoms of Poisoning.—Arsenic poisoning is still prevalent. The drug is taken either with suicidal intent or accidentally, especially by children. Arsenic continues to be one of the chief constituents of rat poisons, insecticides, and fruit and vegetable sprays. The action of arsenic is cumulative, and the symptoms of poisoning may be so insidious that they are recognized with difficulty.

Acute Poisoning.—

1. Difficulty in swallowing.
2. Gastrointestinal pain followed by profuse and violent vomiting.
3. Vomitus may contain shreds of epithelium, mucous, and later blood and bile.
4. Diarrhea which becomes progressively severe, contains shreds of epithelium (rice water stools), mucus, and blood.
5. Scanty urine and finally suppression.
6. Severe muscle cramps
7. Thirst.
8. Shock, coma, death.

Chronic Poisoning.—The symptoms of chronic arsenic poisoning are insidious and difficult to recognize because they simulate the symptoms that attend many disorders. They are weakness, languor, loss of appetite, nausea and vomiting, and diarrhea. Later are symptoms like an acute head cold, watering of the eyes, congested membrane of the nose and throat. Stomatitis and increased flow of saliva as well as dermatitis, scaling of the skin and increased pigmentation, may be found. As poisoning progresses involvement of the nervous system in the form of inflammation of sensory and motor nerves occurs. Aplastic anemia may develop from injury to the bone marrow.

Treatment.—Treatment of poisoning depends upon the length of time that has elapsed since the drug was taken. In acute conditions, prompt lavage, treatment of shock, and use of morphine to control pain are indicated. The extreme loss of body fluids makes this an

The choice of iron compound should be determined largely by the patient's tolerance to the drug and by the way his blood responds to the administration of it. All of the iron compounds are effective if they can be given in large enough dosage. Ferrous sulfate is thought to be utilized to the best advantage of any of the preparations.

Symptoms of Overdosage.—Long-continued administration of iron may cause headache, loss of appetite, gastric pain, nausea, vomiting and constipation or diarrhea. Patients should be forewarned of the possibility of experiencing abdominal cramps and diarrhea when taking iron. If only the latter symptoms develop the drug should be stopped for a day or two and then resumed. If many of the above symptoms develop, it may be necessary to take a longer rest period before resuming the dosage. Tolerance to iron is apparently not developed.

Arsenic

Inorganic arsenic is a general protoplasmic poison and was the favorite tool of professional poisoners of the Middle Ages. The basic mechanism of how cells are injured is not well understood.

Action on—

1. *Circulation.*—Capillary dilatation occurs in all capillary beds but especially in the splanchnic area, resulting in decreased blood pressure and in an escape of plasma from the capillary vessels.

2. *Gastrointestinal Tract.*—The capillary beds are moderately dilated by small doses of arsenic and such changes are associated with increased absorption and secretion. Large doses, however, cause extreme dilatation, hyperemia, exudation of plasma, and the formation of vesicles in the gastrointestinal mucosa. These areas may rupture and the epithelial fragments which are cast off plus the fluid exudate cause the irritation of the bowel and give rise to the so-called "rice water stools." In time, the feces become bloody. Gastrointestinal symptoms tend to come on so gradually that they may not be associated with the action of arsenic.

3. *Kidney.*—The capillaries of the glomeruli dilate, swell, and allow the escape of protein. Varying degrees of necrosis and degeneration may affect the renal capillaries, tubules, and glomeruli.

4. *Skin.*—Arsenic has long been thought to enhance the nutrition of the skin and hair. Prolonged use, however, leads to atrophy and degeneration. Skin eruptions may occur after arsenic administration.

5. *Blood.*—The vascularity of bone marrow is increased. The cellular composition of the blood is altered but the mechanism of this reaction is little understood. The mature forms of red blood cells are

anemia. This type of anemia is characterized by defective formation and maturation of red blood cells which is believed to be due to a deficiency of a specific substance normally made in the stomach and stored in the liver. This substance, although its exact nature is unknown, has proved to be a specific for pernicious anemia. It is called the *antianemic principle*. When the body is deficient in this substance over a period of time, a series of characteristic symptoms and pathologic changes develop. The patient has a peculiar yellowish pallor, complains of weakness, dyspnea, itching, dyspepsia, diarrhea, and sore tongue. Serious changes may also take place in the nervous system. The latter are particularly significant and may include psychoses, optic atrophy, incoordination of movement, loss of vibratory sense, peripheral neuritis, etc. Death may result from the changes associated with pernicious anemia unless the changes are permanently arrested.

Method of Action.—Several factors operate in the formation of the antianemic principle, which is essential for the formation of the red blood cells:

1. An extrinsic factor found in foods such as beef muscle, liver, yeast, wheat germ, eggs, milk, and rice polishings.
2. The intrinsic factor is a substance found in the gastric mucosa and secreted into the gastric juice. In pernicious anemia there is an inability to secrete this substance.
3. The interaction of the extrinsic and intrinsic factors in the gastrointestinal tract with the resulting formation of a substance called the antianemic principle which is absorbed from the intestine.
4. The storage of the antianemic principle in the liver and its release to the blood-forming organs and their utilization of it in blood formation.

Absorption.—The antianemic principle of liver and stomach preparations is absorbed from the intestine, rectum, and parenteral sites of administration. However, thirty to fifty times as much liver must be given orally as parenterally to obtain satisfactory hemopoietic response. To avoid giving large oral doses, investigators sought for an effective concentrate. It has been shown that stomach tissues of animals contain a substance which also has the power to stimulate red cell formation.

Therapeutic Uses.—Liver and stomach preparations are administered in the treatment of anemias in which there is defective red cell formation and maturation. Pernicious anemia is the most important member of this group of anemias. The most effective route of

important factor in the treatment of shock with intravenous fluids. In chronic arsenic poisoning there is no specific treatment but rather the treatment of symptoms as they develop, in addition to finding the source of the drug and stopping its ingestion.

Uses of Arsenic.—Although inorganic arsenic is highly poisonous, organic arsenicals are less toxic to man although very poisonous to certain protozoan organisms. They are employed in the treatment of treponemiasis, trypanosomiasis, and other protozoan infections.

Arsenic is sometimes given for its tonic effect (questionable) and in the treatment of chronic myelogenous leucemia. Arsenic depresses the formation of white blood cells in the latter disease. Arsenic is also one of the drugs used in the treatment of skin disease known as psoriasis.

Preparations.—Arsenic Trioxide, U. S. P., the preparation in which arsenic has been commonly used in medicine. It is an opaque, white powder having a faint, sweet taste and no odor. It is very poisonous. Dosage: $\frac{1}{30}$ gr.

Solution of Potassium Arsenite, U. S. P. (Fowler's Solution), is an aqueous alcoholic solution containing about 1 per cent of arsenic trioxide and potassium bicarbonate. It is often administered in increasing doses until symptoms of mild intoxication appear. The initial dose is usually 1 minim three times a day and this is increased by 1 minim at each administration. A slight toxic action is indicated by nausea, colicky pains or a puffiness under the eyes. Albumin may also be present in the urine. On the appearance of such symptoms, administration of the drug should be discontinued temporarily and started again later with smaller doses.

Sodium Cacodylate, N. F., is the sodium salt of cacodylic or dimethyl arsenic acid. Its action resembles that of other arsenic compounds, but it is much less toxic and less likely to cause undesirable side effects. It has been recommended particularly in pseudoleucemia, anemia, chlorosis, malarial cachexia, etc. As it is sometimes decomposed in the stomach, imparting a garliclike odor to the breath, it is preferable to give it hypodermically or intramuscularly, but this does not always prevent the development of the odor.

The average dose is 0.15 Gm. (2 grains). It is administered hypodermically or intramuscularly in aqueous solution; or by mouth in elixir or in the form of pills.

Liver and Stomach Preparations

Minot and Murphy (1926) demonstrated that the feeding of liver has a marked therapeutic effect in the treatment of pernicious

Solution of Liver (Liquor Hepatis), U. S. P. Dosage: 1 U. S. P. unit. For oral use.

Liver Injection (Injectio Hepatis), U. S. P. Dosage: Intramuscular, 1 U. S. P. unit.

Liver With Stomach (Hepar cum Stomacho), U. S. P. This is brownish powder made from mammalian liver and fresh hog stomach tissue. Average daily dose: 1 U. S. P. unit.

Powdered Stomach (Stomachus Pulveratus), U. S. P. Daily dosage: 1 U. S. P. unit daily. This is the dried and powdered defatted wall of the stomach of the hog.

Ventriculin (Parke, Davis & Co.), N. N. R. This is a stomach preparation which is tested clinically for potency and is given in doses of 20-40 Gm. daily and reduced about one-half for maintenance dosage. For oral use.

Extralin (Lilly), N. N. R. A concentrate from liver and stomach. For oral use. Six grams are equivalent to 1 U. S. P. unit.

For liver oil preparations see Vitamins, p. 451.

One U. S. P. unit of liver extract is the daily amount necessary to produce the maximum reticulocyte response when injected for ten days in a patient with pernicious anemia in relapse.

Since in nearly all cases of pernicious anemia there is absence of hydrochloric acid in the stomach, full doses of the official dilute acid should be given with meals not only to aid digestion but to act as a gastric antiseptic. If possible $\frac{1}{2}$ dram to 1 dram should be administered in sweetened water, but in many cases the tongue is too sore to permit this.

In addition to this treatment, the patient should receive plenty of nourishing food, which is well flavored, varied and easy to digest. It should contain remedies needed by the system, such as bone salts and iron. Red wines are valuable, especially port wine, and the patient should have plenty of sunshine and fresh air.

Whole Blood and Its Constituents

Blood transfusion plays an important although passive role in the treatment of anemic conditions. Transfusions do not apparently stimulate the bone marrow to greater activity but in times of crises they may save the patient's life when the patient cannot wait for the action of iron or liver to become effective.

For blood transfusions to be used satisfactorily it is important that the blood be readily available and of the suitable type. It is also essential that a careful technic be developed and strictly ad-

administration of liver is by intramuscular injection. Response to parenteral liver therapy occurs within a few days and brings about improvement in appetite and strength, and within a week the gastrointestinal symptoms may subside. Complete remission of symptoms may occur within a month. Response following oral administration is much slower and dosage must be much larger. Even with large oral doses the amount of absorption is somewhat uncertain.

Dosage.—The amount of liver or liver extract which must be given to secure a satisfactory hemopoietic response on the part of the patient depends upon the route of administration, the severity of the anemia, and the nature and extent of the changes in the nervous system. Patients with evidence of degenerative changes in the nervous system must have larger and more frequent doses of liver extract than those who do not have this complication. The amount of liver which may be enough to keep the blood normal may be insufficient to prevent continued regression in the nervous tissues. The patient must be encouraged to report at intervals to his physician who is the only one in a position to judge the adequacy of the dosage. The changes in the nervous system must be arrested at all costs. Patients who have once begun the use of liver extract for pernicious anemia must continue its use for the rest of their lives. Small maintenance doses may do very well to keep the symptoms controlled while discontinuance may precipitate a serious relapse from which it may be difficult or impossible to regain all of the benefits of former therapy. Nurses are sometimes in a position to reinforce the advice of the patient's physician when it involves strict adherence to regular administration of the drug even though there are no apparent symptoms of the disease.

For the average patient in relapse, 15 units of antianemic principle may be injected daily for three or four days. Then the same dose may be given two or three times a week until the blood picture is definitely improved, and then once or twice weekly until the blood is normal. The maintenance dose must be determined largely by trial and error, but 15 units every two or three weeks usually suffices.* Oral therapy requires daily dosage. If complications such as infection or nerve changes are present, the dosage may need to be much greater.

Preparations.—

Extract of Liver (Extractum Hepatis) (Dry Liver Extract), U. S. P.

Dosage: 1 U. S. P. unit. For oral use.

*Goodman and Gilman: *A Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 1131.

Hemostatics

Hemostatics or styptics are substances which are used to control hemorrhage. Iron salts, alum, and tannins shorten coagulation time when applied to a bleeding point. Others such as adrenalin, calcium salts, vitamin K, and sodium citrate are effective when administered systemically. Various preparations made from animal tissues are used to promote blood clotting in case of hemorrhage due to faulty coagulation of the blood. They include the serums obtained by coagulating horses' blood and withdrawing the serum; and the substances produced by heating suspensions of fresh ox brain in physiologic salt solution and removing the coagulated protein. These substances all contain either thromboplastin or kephalin, a lipid substance found in brain tissue which has been shown to be identical with thrombin.

2. Blood Depressants

The use of blood depressants is attended by dangers not found in the use of blood stimulants. They include blood-letting as well as drugs which bring about destruction of cellular elements which may be present in excess. Polycythemia rubra (polycythemia vera) is characterized by large numbers of red cells in excess of normal, while abnormal numbers of white cells are found in leukemia.

Phenylhydrazine Hydrochloride is a substance which is able to bring about the destruction of red blood cells. The chemical is non-official and is not included in N. N. R. It is given by capsule orally in doses of 0.2 Gm. daily for several days and then 0.1 Gm. daily until the erythrocyte count and hemoglobin content approach normal and then the patient is placed on a maintenance dose in accordance with his individual needs. Intermittent therapy is usually necessary for the polycythemic patient because the disease is chronic. Phenylhydrazine hydrochloride is a potent drug and may cause much harm unless administered with caution and under conditions where the patient can be carefully observed and where accurate blood studies as well as liver and kidney function tests can be made. Jaundice, nausea and vomiting, skin eruption, and increased tendency to thrombosis are among the chief symptoms of poisoning.

Benzol.—Medicinal benzene has been employed in the treatment of leukemia because it brings about the destruction of white blood cells. The observation that a lowered white cell count appeared in

hered to, in order to help prevent reactions. The blood should be administered slowly, particularly if the patient's anemia is severe. Sometimes one transfusion of whole blood will suffice, but under other conditions a series of small transfusions may accomplish better results.

Transfusions of whole blood are of value not only to replace red cells but also to restore blood volume and thereby blood pressure. The latter value is seen particularly in the treatment of shock. Whole blood, since it contains all of the necessary fluid holding constituents, does not pass out of the vascular system as rapidly as most parenteral fluids.

Blood Plasma.—Blood plasma is the fluid part of the blood which may be procured by separating the blood cells from the whole citrated blood. Plasma may be given irrespective of the donor's group. Many authorities believe that blood plasma, since it contains the blood proteins, sugar, salts, etc., is an ideal transfusion medium to restore effective blood volume in the treatment of peripheral circulatory failure associated with severe burns, traumatic shock, or hemorrhage. Blood plasma can be used as it is for transfusion or it can be concentrated, dehydrated, and stored for long periods of time without deterioration. The addition of sterile distilled water is all that is needed to make it ready for immediate use. Plasma in the dried form is particularly stable and useful when transportation, storage, and contamination are problems that must be considered.

Blood Proteins.—Blood plasma can be further broken down to many useful parts. Albumin is just as effective as plasma in shock treatment and effective treatment requires less of the albumin than of the plasma. Blood albumin was used quite extensively in the war zones where first aid treatment included shock therapy.

Thrombin and fibrinogen can also be separated from plasma and then purified and concentrated into fine white powders. When put into solution they coagulate to form fibrin. The solution is sometimes applied locally to stimulate blood clotting and as a sort of glue in skin grafting.

Red Cells.—Red blood cells, although formerly discarded after they had been separated from the plasma, are now being used for a number of things. They may be transfused into anemic patients or they may be applied locally to infected wounds, burns, and ulcers. In the latter case they serve to speed up the healing process, and at the same time they may bring about relief of pain or aid in recovery from the infection.

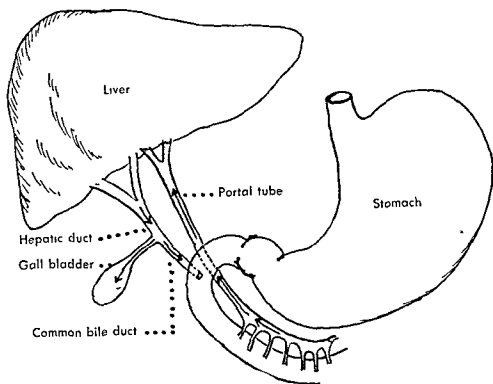


PLATE XII—This diagram represents the pathway of the portal-biliary circulation of bile salts. After their passage into the duodenum, most of them are reabsorbed into the portal blood and are returned to the liver where they are again resecreted. This form of circulation is directly connected with the absorption of fats and fat-soluble vitamins.

employees of industries in which benzol was used first led to its use in leukemia. It has, to a great extent, been discarded because of the danger of producing an aplastic anemia.

3. Blood Coagulants

Explanation of Coagulation.—The action of drugs in hastening or retarding coagulation, act by hastening or retarding the normal processes. These normal processes are not satisfactorily known, but consist in the reactions involved in the formation of fibrin, from its precursor in the blood. The fact that there are four or more theories of coagulation is evidence of incomplete knowledge.

Preparations.—

Brain Lipoid, N. N. R. (Impure Cephalin). An extract of the brain of the ox or other mammal. This preparation may be spread on gauze sponges, on pledgets, or on the tissues themselves; or an emulsion may be prepared by shaking up with physiologic solution of sodium chloride and used in the same way over the tissues *

Thrombin Topical, N. N. R. A preparation of Thrombin, isolated from bovine plasma. It is intended as a hemostatic for topical application to control capillary bleeding.

Solution of Brain Extract, N. N. R. An extract of cattle brain in physiologic salt solution. The solution may be applied directly to the bleeding surface or sprayed on it or applied with a sponge and then pressed on the bleeding surface.

Calcium.—The part which calcium normally plays in blood coagulation has led to its use in hemorrhagic conditions, such as hemophilia, purpura and the intestinal hemorrhage of typhoid fever. It is very improbable that it is effective, since the blood in these conditions always contains plenty of calcium. The preparations usually employed are the chloride and lactate. They may be given by mouth, by hypodermic or intravenously. Calcium chloride occurs as white, translucent crystals having a sharp, saline taste. It is best administered in dilute solution sweetened with syrup or elixir. Calcium lactate is less irritating than the chloride and therefore better adapted for hypodermic use. The average dose of each preparation is 1.0 Gm. (15 grains).

Vitamin K was discovered by Dam of Copenhagen in 1935 as a result of a study of newly hatched chicks which had a fatal hemor-

*N. N. R., 1947, p 328.

hemorrhagic disease. This condition he found could be prevented and cured by the administration of a substance found in hog liver and in alfalfa. It was later discovered that the delayed clotting time of the blood was due to a deficiency of prothrombin content.

Vitamin K is a fat-soluble vitamin and the presence of bile salts in the intestine is essential for its absorption. Vitamin K deficiency is therefore seen in patients with obstructive conditions of the biliary tract.

The discovery of certain synthetic analogues, which greatly resemble the natural vitamin and have even greater physiologic activity, is of therapeutic significance. Some of the analogues are water soluble in which case the administration of bile salts is unnecessary.

Action.—The exact function of vitamin K in the formation of prothrombin is not clear. It is absorbed from the intestine and taken to the liver where it enters into combination with some unknown factor to form prothrombin. To avoid a deficiency of prothrombin in the body, it is apparently essential that certain conditions be maintained: (1) the diet must contain vitamin K or materials from which it may be made, (2) bile salts must be present in the intestine to assure adequate absorption, (3) a normal absorptive surface in the intestine, and (4) a normally functioning liver.

Uses.—Vitamin K is useful only in conditions in which the prolonged bleeding time is due to low concentration of prothrombin in the blood which is not in turn due to damaged liver cells. Vitamin K has been recommended for hemorrhagic conditions in the newborn for which prophylactic doses are administered during the last stages of pregnancy and first few weeks after birth.

It is also indicated in the preoperative preparation of patients with deficient prothrombin, particularly those with obstructive jaundice. Hemorrhagic conditions not due to deficiency of prothrombin are not successfully treated with vitamin K.

The natural concentrates have to a great extent been replaced by the synthetic preparations. It is important that the prothrombin content of the blood be measured frequently when the patient is getting vitamin K. Parenteral preparations should be administered if for some reason the intestinal absorption is impaired.

Preparations.—

Menadione Tablets (Tabellae Menadioni), U. S. P. Dosage: 1 mg. ($\frac{1}{60}$ gr.).



normal rather quickly, and there is danger of sudden clot formation should the drug be discontinued too soon.

Heparin appears to be of particular value in preventing postoperative thrombosis and embolism. It does not help the patient who develops a sudden and massive embolism but it helps to prevent the extension of a thrombus. Patients who have once had a phlebitis or nonfatal embolism are more likely to experience this mishap a second time than those who do not have this type of history, and hence they constitute a group of patients for whom the drug may be used with very satisfactory results.

One of the things which the nurse should be on the watch for in patients receiving heparin is bleeding. This does not apparently occur often, but it may happen and usually means that the drug must be discontinued. The postoperative patient may bleed from the wound or may develop a hematuria. Men patients should not be shaved or be allowed to shave while getting the drug because of the danger of creating a potential bleeding area.

Unfortunately heparin is expensive and its routine use for surgical patients is not feasible. Its cost compares with that of the use of an oxygen tent.

The clinical use of heparin in the treatment of thrombosis and embolism is relatively recent and many aspects of its use await further investigation.

Dicoumarin (Dicumarol).—As a result of the experimental research work done in hemorrhagic sweet clover disease in cattle, a chemical substance has been recognized, isolated, and later synthesized. It is known as Dicoumarin or more recently "Dicumarol." Its therapeutic value has not yet been clearly established, although it appears to hold promise of being a valuable anticoagulant.

Dicoumarin apparently suppresses the formation of prothrombin and thus prolongs the prothrombin time. This activity is seen in vivo but not in vitro. Its effects are not produced as immediately as after the use of heparin, but only after an interval of at least twenty-four hours. Likewise when the drug is discontinued, an interval of time elapses before normal prothrombin and coagulation times are reached.

Dicoumarin seems to have certain decided advantages over heparin as an anticoagulant. It is much cheaper, may be administered orally, and has a more prolonged action. On the other hand, because of its prolonged effect it is controlled with greater difficulty, and yet rapid effects cannot always be secured as speedily as may be necessary to prevent fatal embolism.

Menadione Sodium Bisulfite Injection, U. S. P. Average dose: Intramuscular or intravenous, 2 mg. ($\frac{1}{30}$ gr.)

Various commercial water-soluble preparations are also available.

4. Anticoagulants

Anticoagulants are used mainly for the following: (1) to prevent coagulation of blood which is to be used for transfusion or for laboratory and experimental work, (2) for the preservation of blood, and (3) to prevent postoperative thrombosis and embolism.

Sodium Citrate.—Sodium Citrate is used as an anticoagulant in blood to be used for a transfusion or in blood which is to be stored for a time. The U. S. P. preparations are available in 0.25 per cent solutions of sodium citrate in nonsterile solution, in sterile solution for nonparenteral use, and in sterile solution for parenteral administration. Only the last-mentioned should be used in blood for transfusion.

Heparin Sodium, N. N. R.—Heparin is a purified liver extract prepared by Howell and Holt in 1918 which prolongs the coagulation time of the blood. It is an ideal anticoagulant for use in research and many clinical problems. It acts both *in vitro* and *in vivo*. Its clinical use so far has been limited, but good results are reported by Best in the prevention of thrombosis formation following operations. One milligram per 100 cc. is adequate for the prevention of coagulation. So far as is known, the physical characteristics of the blood are not changed. Its intravenous injection has no effect on blood pressure or respiration, if the product is pure. Heparin acts by preventing the formation of thrombin from prothrombin. It does not prevent the action of thrombin once it is formed.

Hospital patients are treated either by the continuous intravenous drip method or by injections of heparin solution every two or three hours. The former seems to be a favorite method in this country, as it has the advantage of a more constant prolongation of the coagulation time of the blood. The initial response to heparin occurs almost immediately and lasts for a relatively short time unless replenished. The dosage must be determined for each individual patient and maintained at a level which keeps the coagulation time well above normal (15-20 minutes). When heparin is administered intravenously, the rate of flow must be carefully watched and the coagulation time checked several times a day. After being started the administration should continue for a minimum of seven to ten days or longer. When it is stopped the coagulation time returns to

normal rather quickly, and there is danger of sudden clot formation should the drug be discontinued too soon.

Heparin appears to be of particular value in preventing postoperative thrombosis and embolism. It does not help the patient who develops a sudden and massive embolism but it helps to prevent the extension of a thrombus. Patients who have once had a phlebitis or nonfatal embolism are more likely to experience this mishap a second time than those who do not have this type of history, and hence they constitute a group of patients for whom the drug may be used with very satisfactory results.

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The administration of this drug must be carefully controlled to avoid dangerous hemorrhage. The prothrombin time must be determined frequently (daily). Some investigators recommend that dicoumarin be administered so as to keep the prothrombin time between 35 and 60 seconds. Because of the danger of hemorrhage it is important to have at hand some means of controlling the effect of dicoumarin, should bleeding occur. Transfusions of whole blood or blood plasma will reduce the prothrombin time effectively.

When a rapid as well as prolonged anticoagulant effect is desired, heparin may be given along with the dicoumarin. Then when the effect of the dicoumarin is adequate the heparin may be discontinued.

Dicoumarin appears to be of value not only in the treatment but also in the prevention of postoperative thrombophlebitis and pulmonary embolism. Its administration should be continued for several weeks.

Dosage of this drug must be determined largely in relation to individual patients. The drug is obtainable in 100 mg. capsules. Some investigators advocate giving the patient 300 mg. on the first day; 200 mg. on the second day, and each day thereafter that the prothrombin time is less than 35 seconds.

Dicoumarin is contraindicated in all patients who already have a prolonged prothrombin time and usually in patients who have ulcerating lesions or for those who have subacute endocarditis.

5. Drugs Which Increase Alkalinity or the Alkaline Reserve

The greatest alkalinity that is compatible with life is pH 7.9 and the lowest is pH 7. The buffer substances of the blood are better able to control acids than to take care of excess base which may move into the blood stream. All of the base that is combined with carbon dioxide in the form of bicarbonate is potentially available for the neutralization of acid and constitutes our alkaline reserve. The amount of base in this form is not measured directly but rather the amount of carbon dioxide that the blood will hold when saturated is determined. This is known as the carbon dioxide combining power and is normally estimated to be 50 to 75 volumes per cent or 50-75 cc. of carbon dioxide in 100 cc. of blood plasma.

Causes of Acidosis.—A depletion of the alkaline reserve of the blood and the appearance of the so-called "acetone bodies" constitute a condition known as acidosis. This does not mean that the blood is acid in reaction. If the alkaline reserve is depleted but the pH does not change, the acidosis is said to be compensated; if the pH

begins to change, the acidosis is uncompensated and the condition is correspondingly more serious. Severe acidosis may occur in (1) diabetes, (2) nephritis, (3) severe dehydration and starvation, (4) following the administration of strong acids (poisons) or acid salts, (5) following severe burns or any condition in which the excretory channels of the body do not function normally.

The Treatment of Acidosis.—The administration of citrus fruits which in the body break down to form carbonates and bicarbonates in the blood is usually sufficient in the treatment of a mild acidosis. In a severe acidosis as may accompany diabetic coma, insulin and glucose may be employed. Glucose solutions are also given to treat the acidosis which accompanies severe dehydration, starvation, or postanesthetic shock. Acidosis is further treated with sodium or potassium acetate, and sodium or potassium citrate as well as sodium bicarbonate.

When the sodium bicarbonate of the blood is reduced, much may be taken by mouth before the urine becomes alkaline. Sellard devised from this a simple test: In the majority of normal persons, 5 to 10 grams of sodium bicarbonate alkalinizes the urine. If more is required, the alkali reserve of the body is below normal.

6. Drugs Which Decrease Alkalinity

Alkalosis is a condition in which there is excessive alkalinity of the body fluids. This may result from the excessive intake of alkalies such as sodium bicarbonate, calcium deficiency, lack of absorption of acid ions from the gastric secretion, or hyperventilation. The treatment may consist of giving abundant fluids, intravenous injections of normal saline solution and acid salts, such as ammonium chloride and sodium acid phosphate.

Questions for Review

1. What constitutes a heart stimulant?
2. How would you describe a patient who has myocardial insufficiency?
3. Explain the terms: myocardial insufficiency, fibrillation, heart block.
4. What results might you expect if such a patient were given digitalis. Explain why you might expect these results.
5. Why is tincture of digitalis given by mouth? How would you expect to administer tablets of digitalis leaves? Ampules of digalen?
6. What general nursing care would be necessary to aid the action of drugs in the treatment of heart conditions?
7. Why is it usually necessary to keep a careful record of the intake and output of fluids for a patient who is receiving digitalis?
8. Why is it important to count the pulse before administering the next dose of digitalis?

The administration of this drug must be carefully controlled to avoid dangerous hemorrhage. The prothrombin time must be determined frequently (daily). Some investigators recommend that dicoumarin be administered so as to keep the prothrombin time between 35 and 60 seconds. Because of the danger of hemorrhage it is important to have at hand some means of controlling the effect of dicoumarin, should bleeding occur. Transfusions of whole blood or blood plasma will reduce the prothrombin time effectively.

When a rapid as well as prolonged anticoagulant effect is desired, heparin may be given along with the dicoumarin. Then when the effect of the dicoumarin is adequate the heparin may be discontinued.

Dicoumarin appears to be of value not only in the treatment but also in the prevention of postoperative thrombophlebitis and pulmonary embolism. Its administration should be continued for several weeks.

Dosage of this drug must be determined largely in relation to individual patients. The drug is obtainable in 100 mg. capsules. Some investigators advocate giving the patient 300 mg. on the first day; 200 mg. on the second day, and each day thereafter that the prothrombin time is less than 35 seconds.

Dicoumarin is contraindicated in all patients who already have a prolonged prothrombin time and usually in patients who have ulcerating lesions or for those who have subacute endocarditis.

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The greatest alkalinity that is compatible with life is pH 7.9 and the lowest is pH 7. The buffer substances of the blood are better able to control acids than to take care of excess base which may move into the blood stream. All of the base that is combined with *carbon dioxide in the form of bicarbonate is potentially available* for the neutralization of acid and constitutes our alkaline reserve. The amount of base in this form is not measured directly but rather the amount of carbon dioxide that the blood will hold when saturated is determined. This is known as the carbon dioxide combining power and is normally estimated to be 50 to 75 volumes per cent or 50-75 cc. of carbon dioxide in 100 cc. of blood plasma.

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4. The codeine was ordered:
 - a. to put the patient to sleep -----
 - b. to make the pulse slower and stronger -----
 - c. to assist in decreasing edema by increasing the urine output -----
 - d. to relieve discomfort and thus help to decrease the strain on the heart -----
5. The expected action of the digitalis leaf is:
 - a. stimulation of the vagus mechanism -----
 - b. stimulation of the glomeruli of the kidney -----
 - c. decreased activity of the bundle of His -----
 - d. increased power of myocardial contraction -----
6. Symptoms which may indicate cumulative action of digitalis:
 - a. marked increase in urine output -----
 - b. pulse rate below 60 -----
 - c. nausea and vomiting -----
 - d. diarrhea -----
7. If any of the above symptoms develop you would:
 - a. stop the drug immediately -----
 - b. give the drug and report the symptoms to the head nurse -----
 - c. give the drug and chart the symptoms so that the doctor will see the record -----
 - d. withhold the drug until the doctor knows of the symptoms and then proceed according to his further directions -----

State reason for your choice in (7).
8. Points in nursing care which if carried out will assist these drugs in obtaining desired results:
 - a. provision of plenty of fluids -----
 - b. provision for accuracy in records of intake and output -----
 - c. provision for all factors possible which promote physical and mental rest -----
 - d. provision for accurate counting of the pulse before the administration of each dose of digitalis -----

Sample Test Situation No. II

Mrs. D. was admitted acutely ill with extreme pain in the upper right quadrant and vomiting, the vomitus containing a large amount of bile. A diagnosis of biliary colic was made. Orders, written at 1:30 P.M., for the patient included:

1. Atropine sulfate, gr. $\frac{1}{100}$ (H) stat.
2. Nitroglycerin, gr. $\frac{1}{100}$ sublingually
S.O.S. if the pain returns

The patient felt much better by 2:30 P.M., but again complained of pain at 4:00 P.M.

In regard to the above situation certain statements follow. Place a check after those which are the best answers.

1. When the patient complained of pain at 4:00 P.M. you would:
 - a. Immediately dissolve nitroglycerin, gr. $\frac{1}{100}$, in about one-half ounce of water and have the patient take it -----
 - b. give the patient an alcohol rub, change her position, and tell her that if this does not relieve the pain you will later give her a medication -----

9. What is meant by digitalization of a patient?
10. Why are organic rather than inorganic preparations of iron frequently preferred for the treatment of anemia?
11. Give the preparations and doses of digitalis suitable for hypodermic administration.
12. What are the symptoms and treatment of cumulative digitalis poisoning?
13. When is the use of strophanthin indicated? Give the dosage.
14. Define heart depressant.
15. Name several vasodilators and vasoconstrictors and explain how they accomplish their effects.
16. Explain why patients receiving some form of iron are likely to complain of constipation after a week or two. Why may they also complain of nausea?
17. What advantages do the more recent preparations of liver have over the older methods of preparing it?
18. Why should you encourage a patient to keep on taking liver when he says he feels much better and sees no need of spending the money, even though the doctor has told him that he will need to take liver the rest of his life?
19. What laboratory reports will help you understand whether or not your patients with circulatory diseases are making satisfactory progress?
20. What are some of the dangers associated with the use of anticoagulants?

Sample Test Situation No. I

Mrs. Black, aged 70 years, was admitted at 10:30 A.M. with a diagnosis of advanced arteriosclerosis and decompensated heart. She is edematous, cyanotic, has considerable dyspnea, rapid pulse which is weak and irregular. She is very nervous and restless. The doctor's orders include:

1. Phenobarbital	gr. ss t.i.d.
2. Digitalis leaf	gr. iss q 3h.
3. Codeine	gr. 1 (h) q 4 h. p.r.n.
4. Seconal	gr. iss h.s.

In relation to the above situation, place a check after the part or parts of statement below which in your judgment is the best answer.

1. Phenobarbital was ordered as:
 - a. an analgesic
 - b. a cardiac depressant
 - c. a sedative
 - d. a hypnotic
2. The drug which should be given first after admission is:
 - a. phenobarbital
 - b. digitalis
 - c. codeine phosphate
 - d. seconal

Give reason for your answer.
3. The approximate hour at which the seconal should be given is:
 - a. when the patient is ready for an afternoon nap
 - b. at 6:30 P.M.
 - c. at 10:30 P.M.
 - d. at 8:00 P.M.
 - e. Sometime during the night if patient is unable to sleep

4. The codeine was ordered:
 - a. to put the patient to sleep -----
 - b. to make the pulse slower and stronger -----
 - c. to assist in decreasing edema by increasing the urine output -----
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 - e. Sometime during the night if patient is unable to sleep -----

8. Nitroglycerin was ordered because:

- a. the doctor had ascertained that the patient was suffering from angina pectoris -----
- b. the nitroglycerin would relax the common and cystic duct by direct depression of the smooth muscle in the duct and thus relieve the colic -----
- c. the patient needed a heart stimulant -----
- d. the nitroglycerin depresses the motor areas in the cerebrum and thus would relax the duct and relieve the colic -----

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- c. wait at least until 4:30 P.M. to see if the pain becomes severe enough to warrant medication -----
- d. immediately obtain nitroglycerin, gr. $\frac{1}{100}$, and have the patient place the tablet underneath the tongue and leave it there until dissolved -----
- e. immediately obtain the ampule containing nitroglycerin, gr. $\frac{1}{100}$, break it in a piece of gauze and hold it near the patient's nose so that the fumes can be inhaled -----
- 2 If the patient complained of the bitter taste of nitroglycerin you would: -----
 - a. say nothing -----
 - b. allow the patient to rinse her mouth -----
 - c. allow the patient to drink a small amount of water with the drug in her mouth -----
 - d. if you would do none of these, make a statement as to just what you would do -----
- 3 The atropine was given to the patient -----
 - a. in order to relieve pain -----
 - b. in order to lessen nervous excitement -----
 - c. in order to check the amount of bile in the vomitus -----
- 4 The expected action of atropine would be: -----
 - a. direct depression of smooth muscle -----
 - b. paralysis of the myoneural junction of the parasympathetic nerves -----
 - c. depression of sensory areas of the cerebrum -----
- 5 The expected results of the action of atropine would include: -----
 - a. dilation of the pupil -----
 - b. decreased vomiting -----
 - c. decreased alertness -----
 - d. decreased reflex activity in voluntary muscles -----
 - e. decreased peristaltic activity in cystic and common ducts -----
 - f. thirst -----
 - g. relief of colic pain -----
 - h. perspiration becoming profuse -----
- 6 After administering the atropine you would: -----
 - a. record time, name and amount of drug, method of giving, and nurse's name on the bedside notes -----
 - b. record time, name and amount of drug, doctor's and nurse's name, and date on the opiate sheet -----
 - c. record that drug had been given, the time and nurse's name on the doctor's order sheet -----
- 7 The synergistic effects of atropine and nitroglycerin include -----
 - a. decreased peristaltic activity in cystic and common ducts -----
 - b. flushing of the face and neck -----
 - c. increased amount of perspiration -----
 - d. constriction of the visceral blood vessels -----
 - e. lower blood pressure -----
 - f. an increase in the rate of the heartbeat -----
 - g. decreased nausea and vomiting -----

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UNIT VI

CHAPTER XV

PHARMACOLOGY AS RELATED TO THE RESPIRATORY SYSTEM

Respiration is a characteristic of life. The essential part consists in the absorption and utilization of oxygen and the elimination of carbon dioxide. The respiratory system in man includes: the nasal cavity, the larynx, trachea, bronchi, lungs, the striped and unstriped muscles of the larynx, intercostal muscles and diaphragm, the respiratory center in the medulla, and the blood.

SIGNIFICANT POINTS OF ANATOMY AND PHYSIOLOGY

The Respiratory Center.—Respiration is under the control of a respiratory center in the medulla. This consists of an ill-defined group of cells in the reticular substance over an area bounded by the nucleus of the facial nerve, anteriorly, and by the calamus scriptorius below. It is bilateral, but connecting so that half a center may suffice for the continuation of bilateral respiratory movements. This center is very sensitive to changes in carbon dioxide tension. The slightest rise in carbon dioxide increases respiration. Carbon dioxide acts as a hormone to respiration, and the center tends to keep the carbon dioxide tension of the blood constant.

Carbon dioxide is the chief respiratory hormone. Inhalation of 1.74 per cent carbon dioxide in the respired air increased respiration 43 per cent. Inhalation of 4 per cent carbon dioxide increased respiration 177 per cent. Inhalation of 6 per cent carbon dioxide increased it 500 per cent (Haldane and Priestly).

The Lungs.—The lungs may be regarded as elastic, membranous sacs whose interior is in free communication with the outside air. The alveolar sacs are branches of the trachea > bronchi > bronchioles > alveolar sacs. The bronchiolar musculature is regulated by bronchoconstrictor fibers in the vagi and bronchodilator fibers in the sympathetic. The wall of each alveolus is composed of a single layer of respiratory epithelium. Across this layer and the endothelium of the capillaries, gaseous exchange occurs between the inhaled air and the blood. The total number of alveoli in the lungs of

man has been estimated at about 725,000,000, and their total surface at about two hundred square meters, or 100 to 130 times the surface area of the body. The surface area of the capillaries of the lungs is estimated to be about 90 square meters. The factor of safety, which may be taxed in pneumonia, is quite large.

Functions of Respiration.—The chief functions of respiration are: (1) to supply oxygen to the body and to remove carbon dioxide; (2) it aids also in evaporation of water in the respiratory passages, and this assists in the regulation of the body temperature. This function is more important in animals like the dog, which have no sweat glands, than it is in man. In rise of temperature, as in man, however, increased respiration is a compensating factor.

Gaseous Exchange in the Lungs.—The interchange of gases between the outside air and the blood depends on (1) the difference in tension of the gases, (2) the rate of blood flow through the lungs, (3) the area of the lungs, and (4) the resistance offered by the alveolar walls to the diffusion of gases. The tension of the gases depends on the composition of the air inspired and upon the rate and volume of inspiration. A man at rest may inspire 6 to 8 liters of air per minute, breathing 14 times per minute, while an athlete in maximal effort may inspire 30 times that volume, and breathe 4 to 5 times as rapidly. This shows the great adaptive power of the respiratory mechanism.

CLASSIFICATION OF DRUGS ACTING ON THE RESPIRATORY SYSTEM

A. Drugs which act on the respiratory center. This class includes stimulants and depressants or sedatives.

B. Drugs which affect the mucous membrane lining of the respiratory tract; namely, demulcents, antiseptics, and expectorants.

C. Drugs which affect the size of the bronchioles.

A. DRUGS WHICH ACT ON THE RESPIRATORY CENTER

1. By Direct Stimulation

The most important stimulants are carbon dioxide, caffeine, strychnine (in some instances), atropine, camphor, metrazol, and coramine.

Carbon Dioxide.—Carbon dioxide is a colorless, odorless gas which is heavier than air. It functions in the physiologic control of the respiratory center and can be used as a valuable respiratory stimulant. Whether it affects the respiratory center directly or by

increasing the hydrogen ion concentration is not entirely agreed upon. The fact remains that inhalation of carbon dioxide increases both the rate and the depth of respiration.

Carbon dioxide gas has come to a place of ever-increasing importance in the field of therapeutics. When administered in from 2 to 5 per cent concentrations, it exerts a marked effect on the respiratory center. Inhalation of a 3 per cent concentration doubles the pulmonary ventilation and may be used to relieve Cheyne-Stokes breathing. In 5 to 7 per cent, mixed with oxygen, it may be used before, during, or after anesthesia. In the beginning it speeds up anesthesia by increasing pulmonary ventilation. By lessening the sense of asphyxiation, it reduces struggling. After the anesthesia, it hastens the elimination of ether.

Uses.—1. Carbon dioxide is used as a respiratory stimulant in the treatment of asphyxia of all types. This includes asphyxia neonatorum, carbon monoxide poisoning, cases of drowning, etc. For this purpose it is administered along with a high concentration of oxygen.

2 Carbon dioxide is used a great deal during and after anesthesia where it is useful to combat respiratory depression due to hyperventilation or excessive depression of the respiratory center.

3. Inhalation of carbon dioxide and oxygen mixtures is also thought to be effective in the treatment of postoperative hiccough. Relief of hiccough is apparently accomplished by stimulating the respiratory center and by making the contractions of the diaphragm more regular.

4. Postoperative pneumonia and its complications are believed to be prevented, at least in part, by increasing the depth of breathing and by preventing congestion in the lungs.

Administration.—Carbon dioxide may be administered by means of a close-fitting mask, the gas coming from a storage tank. The patient should inhale the mixture until the depth of respirations is definitely increased which is usually in about three minutes. For the postoperative patient the procedure should be repeated every hour or two for the first forty-eight hours, and then several times a day for several days.

Another way of administering carbon dioxide is to allow the patient to hyperventilate. A paper bag is held over the patient's face and he thus reinhales his expired air in which the carbon dioxide content is continually increased.

Signs of overdosage are dyspnea, breathholding, markedly increased chest and abdominal movements, nausea and increased sys-

tolie blood pressure. The administration of the gas should be discontinued when these symptoms appear. The administration should, in fact, be stopped as soon as the desired effects on respiration have been secured.

The following respiratory stimulants have been discussed in greater detail under the chapter heading "Pharmacology as Related to the Nervous System."

Atropine.—Atropine has some action as a respiratory stimulant because it produces stimulation of the medullary centers. Ordinary therapeutic doses, however, seem to affect only the vagal center and the respiratory center, the latter to a mild degree. The rate and occasionally the depth of breathing are increased. When respiration is markedly depressed, atropine cannot be depended upon to produce stimulation of the respiratory center since large or continued doses of atropine may actually further depress the respiratory center.*

Atropine is commonly given with morphine in hypodermic injections to lessen the effect of the latter drug on respiration, as well as to check the secretion of mucus

Caffeine.—Caffeine when given in large doses or when given parenterally definitely stimulates the respiratory center. The effect is especially noticeable after the respiratory center has been depressed, as from morphine. It is probably one of the most frequently used respiratory stimulants. Tolerance to caffeine which is established in many individuals is a disadvantage in the use of the drug as a respiratory stimulant.

Metrazol.—Metrazol is said to be of value in emergencies due to cardiovascular collapse, in shock, in respiratory failure, and in narcotic depressions.† Metrazol has come into extensive use in the treatment of mental disorders in doses which cause convulsions.

Nikethamide (Coramine).—Nikethamide apparently has its most marked effect upon the respiratory center when the center is in a state of depression. When used on experimental animals, the medullary centers give evidence of stimulation, resulting in increased rate and depth of respiration and peripheral vasoconstriction.

2. By Reflex Stimulation

Usually respiration is increased by stimulation of the skin nerves and the endings of the olfactory and trigeminal nerves of the nose. Stimulation of the sciatic or almost any sensory nerve may stimulate

*Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 463.

†New and Nonofficial Remedies, 1944.

respiration markedly. This explains why a dash of cold water may revive a fainting person or cause a newborn infant to inspire suddenly. It also explains the use of smelling salts or the dilatation of the anal sphincter as an emergency measure when a patient stops breathing.

Camphor, ammonia, and carminatives act as mild respiratory stimulants when taken by mouth. Ammonia, however, is the only drug given by mouth or inhalation for its action as a reflex respiratory stimulant.

Ammonia.—Ammonia when inhaled exerts a local irritation on the mucous membranes of the nose, throat, and lungs, thus causing a reflex stimulation of respiration and a temporary stimulation of the heart action. When taken by mouth the mucous membrane of the stomach is irritated to some extent, gastric acid is neutralized, and gas formation may be checked.

The inhalation of strong ammonia fumes causes intense irritation and swelling of the larynx which may result in asphyxia. If a strong solution of ammonia water (household ammonia) is swallowed, there is extensive destruction of the mucous membrane in the esophagus which may be followed by a stricture. Large doses cause coma or convulsions, collapse, and depression of the respiratory center.

There are two types of ammonia salts, those which liberate ammonia and those which act as a salt. Ammonium carbonate and ammonium chloride are used chiefly as expectorants and diuretics. Ammonia is used as a heart and respiratory stimulant in the form of Aromatic Spirits of Ammonia, U. S. P., 2-4 cc. in half a glass of water. It is the type of stimulant which could be safely kept in the home medicine chest. It would be suitable as a stimulant for treatment of fainting.

Respiratory Depressants or Sedatives

The most important respiratory depressants are the central depressants of the opium group and those of the barbiturate group of drugs. These drugs depress the respiratory center, thereby making the breathing slower and more shallow and lessening the irritability of the respiratory center. Respiratory depression, however, is seldom desirable or necessary, although it is sometimes unavoidable. It is sometimes a side action in otherwise very useful drugs. Occasionally a cough is so painful or harmful that an opiate is administered to inhibit the rate and depth of respiration. A greater value, however, lies in their ability (codeine) to depress the cough reflex.

B. DRUGS WHICH AFFECT THE MUCOUS MEMBRANE LINING OF THE RESPIRATORY TRACT

PREPARATIONS TO RELIEVE COUGH

Demulcents

Respiratory demulcents are sticky substances which protect the lining of the respiratory tract from the irritation of contact with air, and thus check coughing. They are also used as vehicles for other drugs. The most common are syrup of acacia, the mucilage and troches of slippery elm, the mucilage of sassafras, and licorice or glycyrrhiza.

Home remedies include simple syrup, honey, or horehound candy. The soothing effect of steam inhalations upon irritated mucous membranes is also a well-known demulcent. Plain steam or medicated steam may be administered with a special apparatus or by placing a basin of hot water over a hot plate so that the resulting humidity of the room atmosphere is appreciably increased. There is little value, however, in administering steam when the doors or windows are open. Therefore if the patient is to have the benefit of moisture-laden air which will in turn soothe the irritated respiratory tract, it is important to keep the doors and windows of the patient's room closed. The addition of some aromatic substance such as tincture of benzoin, menthol, or oil of pine may make the inhalation more pleasant or soothing.

Nebulae (Sprays)

These preparations often consist of light liquid petrolatum in which are dissolved various aromatics and other medicaments. Liquid petrolatum containing 1 per cent each of menthol and eucalyptol is a common prescription. Nebulae are employed in atomizers for carrying the medicaments into the nose, throat, and trachea.

The N. F. nebulae are:

Nebula Aromatica—contains phenol, menthol, thymol, camphor, benzoic acid, eucalyptol and methyl salicylate and the oils of cinnamon and clove.

Nebula Ephedrinae—contains 1% ephedrine with 0.2% methyl salicylate.

Nebula Ephedrinae Composita—contains 1% ephedrine with camphor, menthol and oil of thyme.

Nebula Mentholis Composita—contains menthol, camphor, methyl salicylate, and eucalyptol.

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is, those that depress and nauseate the patient—are usually those that cause the greatest amount of secretion. This is caused by a relaxation of the mucous membranes and a dilation of the vessels. The stimulating expectorants are those that tone up the patient or the mucous membranes and may diminish secretion.

The Theory of the Use of Expectorants.—Experimentally, little is known of their mode of action, but clinical experience attests their value. They are used empirically to modify the physiology of the respiratory passages. These passages are lined with ciliated epithelium which normally carries secretions of the tract towards the exterior. Mucus that becomes thick and tenacious probably interferes with these ciliated movements and coughing results. We do not know whether or not expectorants modify these movements.

Sedative Expectorants increase the secretion of mucus and thus protect the irritated mucous membrane and lessen the amount of coughing. A dry unproductive cough only wastes the patient's energy. An increased secretion of mucus may result in a productive cough and make the paroxysms of coughing less frequent.

Ammonium Chloride, U. S. P., is frequently administered in some vehicle such as Syrup of Wild Cherry, Syrup of Citric Acid, or Syrup of Orange. Its exact method of action which results in increased mucus secretion is not agreed upon. Ammonium Chloride is given in doses of 0.3 Gm. (5 grains) every hour or two in some suitable medium. It should be accompanied by a full glass of water because the increased fluid intake plays a part in the formation of increased mucus.

Ammonium Carbonate, U. S. P., acts very similarly to ammonium chloride, except that it causes gastric distress more easily. It is given in much the same manner and dosage as ammonium chloride. It is an alkaline salt and cannot be given in acid syrups.

Antimony Potassium Tartrate (Tartar Emetic), U. S. P., occurs as a white powder or as colorless transparent crystals. The drug is irritating to the gastrointestinal tract and, in large doses, causes nausea and vomiting with marked prostration. Tartar emetic is employed for its expectorant action in the first stage of acute laryngitis and bronchitis. For this purpose, small doses should be used, beginning with 0.001 Gm. ($\frac{1}{60}$ grain), which may be repeated hourly, until slight nausea occurs. The drug should then be discontinued to avoid too great depression.

Iodides (Sodium Iodide, U. S. P., and Potassium Iodide, U. S. P.).—Iodides are said to increase the bronchial secretion in subacute and chronic bronchitis. They are too irritating to be used in acute inflammatory conditions of the respiratory tract. When sputum

Light liquid petrolatum acts as a protective. The aromatics are slightly anesthetic and constrictive. Ephedrine is a vascular constrictor and opens the air passages.

Nasal sprays may also contain epinephrine, benzedrine, synephrine or neo-synephrine for their effects on congested mucous membrane. Nasal douching and spraying is not approved by many physicians because of the danger of their overuse. Too frequent interference with the vasomotor mechanism in the nose may do more harm than good, and there is always the possibility of spreading the infection deeper into the sinuses or to the middle ear. Sprays and nose drops are of benefit when judiciously used under the advice of the physician in charge.

Local anesthetics such as cocaine or its substitutes may be applied locally by spraying or swabbing on the mucous membrane.

Antiseptics

It is difficult to find an antiseptic for use in the respiratory tract which is able to kill microorganisms without injuring the mucous membrane. Pulmonary antiseptics which have been used include creosote, guaiacol, and benzoin. However, their antiseptic value is doubtful. Their chief value seems to lie in their ability to lessen the fetid odor of the breath in some cases of bronchitis. Infections of the nose and throat are also treated with sulfonamide drugs whose action comes after absorption. Gargles may contain a number of antiseptic substances such as boric acid, sodium perborate, and potassium chlorate. Warm normal saline solution is probably as effective as most of the gargles commonly employed.

Expectorants

Expectorants are drugs which increase, liquefy or modify the secretion of mucus in the bronchi, and facilitate the expulsion of sputum. They are therefore used in the treatment of coughs, bronchitis, and pneumonia. They are divided arbitrarily into stimulating and sedative or nauseating expectorants. The so-called stimulating expectorants are usually more or less volatile substances which are eliminated by the lungs and the respiratory mucous membranes, upon which they exert a stimulant action during their excretion.

It should be especially noted that the terms *stimulating* and *depressing* refer to the action of the drug on the patient and on the mucous membrane directly, and are not judged by the amount of secretion produced. For example, the depressing expectorants—that

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Eucalyptol, U. S. P., is an organic compound derived from the oil of eucalyptus, which it resembles in appearance, actions and uses. The dose of eucalyptol is 0.3 cc. (5 minims).

Oil of Turpentine, N. F., is a volatile aromatic substance which is useful as a stimulant expectorant in chronic inflammatory conditions of the bronchial passages. It may be administered in steam inhalations in which 1 teaspoonful is added to a pint of the boiling water and the steam inhaled.

Benzoin, U. S. P., is the balsam or aromatic resin obtained from the *Styrax Benzoin*, a Peruvian tree. It is used in the form of the Compound Tincture of Benzoin as a soothing application to inflamed mucous membrane of the throat and bronchi and as a stimulating expectorant. It is usually administered by adding a teaspoonful to a glass of boiling water and inhaling the vapor.

Atropine, although not classed as an expectorant, may be given to check secretion and excessive expectoration in certain forms of bronchitis.

Drugs such as atropine paralyze the effector gland cells and thus prevent secretion by the mucous glands, while drugs which stimulate secretory glands, like pilocarpine, cause a great increase. Unfortunately those drugs which affect cells in the bronchial or respiratory mucous membranes act also on similar structures in all other locations, as the heart, and for this reason their use as expectorants is limited.

Many of the remedies used to break up colds contain atropine. Morphine, codeine, and papaverine act not only as sedatives, but also tend to dry the mucous membranes. In many cases the treatment of a cold or inflammation of the respiratory mucous membranes can best be accomplished by extra rest, tonics, and dieting; for example, the cough of tuberculosis is little aided by the use of expectorants, while proper food availeth much.

Summary of Expectorants

1. EXPECTORANT VEHICLES

Expectorants are usually prescribed in liquid form. Some of the most used vehicles are:

Syrupus Acidi Citrici
Syrupus Tolu
Syrupus Pruni Virginianae
Syrupus Picis Pini
Syrupus Scillae

The dose of these vehicles is 1 to 2 teaspoonfuls.

becomes particularly tenacious, they are given to fluidify the secretion or "loosen the cough." The average expectorant dose is 0.3 Gm. (5 grains) three times a day but quantities up to 2 Gm. (30 grains) may be given. The salts may be administered in a saturated solution or they may be administered in a cough mixture.

Syrup of Hydriodic Acid, U. S. P., may also be given either alone or in a fruit syrup. The adult dose is 4 cc. and may be given every three or four hours. If long continued, these drugs frequently produce symptoms of iodism. These are due to irritation of the nasal passage, the bronchi and skin, and include coryza and pain in the region of the frontal sinus, and various skin eruptions, generally of a papular character. When such toxic symptoms occur, the drug should be discontinued, but may be resumed in smaller doses after the disappearance of the symptoms.

Ipecac, described elsewhere as an amoebicide, when given in small doses is said to promote secretions in the respiratory tract. Syrup of Ipecac, U. S. P., is prescribed in doses of 0.5-1 cc. for adults and 5 minims for infants of one year. A small increase of dosage is made for each additional year. It is used to increase secretions and relieve bronchitis associated with croup.

Stimulating Expectorants tend to diminish secretions but they promote repair and healing in the bronchial mucosa. Some are aromatic substances and some are mild irritants.

Terpin Hydrate, N. F., occurs as colorless, lustrous crystals, nearly odorless, having a slightly aromatic and somewhat bitter taste. Terpin hydrate is antiseptic, diaphoretic and diuretic in action, but is used chiefly to lessen secretion in bronchitis accompanied by free secretion. Average dose of Terpin Hydrate Elixir: 4 cc. (1 fluidram). It may be administered in the form of powder or in capsules. The solution, usually in the form of an elixir, requires an excessive amount of alcohol.

Oil of Eucalyptus, U. S. P., is a volatile oil distilled from the fresh leaves of the *Eucalyptus Globulus*, or blue gum tree which grows in southern countries. It occurs as a colorless or pale, yellow liquid, having an odor resembling that of camphor, and a pungent, spicy taste. It is practically insoluble in water.

Oil of Eucalyptus is used either internally or locally as an antiseptic and expectorant. For local application to the mucous membranes of the nose and throat, it is employed either in the form of oil sprays or as inhalations of vapor from boiling water. For internal use, oil of eucalyptus is given in capsules. The dose is 0.5 cc. (8 minims).

is under considerable pressure the tanks must be handled carefully so as to prevent their falling, or bumping into each other or into anything which may cause undue jarring.

Effects of Oxygen Deficiency in the Body.—Recent experiments in the use of oxygen in airplane travel at high altitudes have resulted in interesting observations of oxygen deficiency in otherwise normal individuals. It has long been known that deprivation of oxygen leads rapidly to death. Tissue cells must have a continuous supply since no provision is made for storage of oxygen in the body. Symptoms of anoxemia begin when the oxygen pressure of inspired air is 14 per cent of that at sea level.*

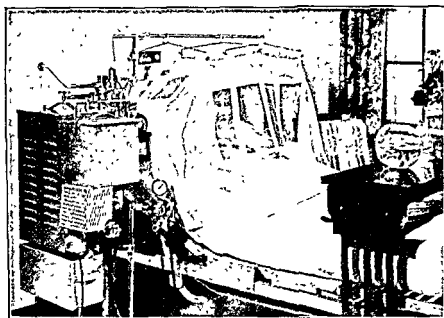


Fig. 22—Oxygen tent in position. Oxygen is introduced into the cabinet at a rate which provides for the desired concentration. The tent also serves as a small air-conditioning unit.

The individual may experience headache, excessive sleepiness, great lassitude, mental inefficiency, irritability, change in pulse and respiration, great fatigue, muscle incoordination, and finally unconsciousness. The cortical cells of the brain are the ones most sensitive to oxygen deficiency and the ones most likely to suffer irreparable damage. The depression of nerve tissue continues downward as the oxygen deficiency continues until finally vital centers in the medulla are affected.

Effect of High Concentrations of Oxygen.—Although high concentrations of oxygen may be breathed, the composition of the blood

*Lovelace, W. R., Jr.: Oxygen for Therapy and Aviation: Proceedings Staff Meeting, Mayo Clinic 15: 647, 1938.

2. SIMPLIFICATION OF EXPECTORANTS

1. To liquefy expectoration—		
Ammonium Chloride	0.5 Gm.	8 gr.
Potassium Iodide	0.5 Gm.	8 gr.
2. Against excessive secretion—		
Terpin Hydrate	0.15 Gm.	2 gr.
Elixir Terpin Hydrate	4 cc.	1 fl. dr.
3. Against coughing and irritation—		
Codeine	3 mg.	½ gr.
Elixir of Terpin Hydrate and Codeine	4 cc.	1 fl. dr.
4. To dry up excessive secretion of nose and mouth—		
Atropine Sulfate	1 mg	⅓ gr.

3. EXPECTORANT MIXTURES

1. Compound Opium and Licorice Mixture (brown mixture) (<i>Mistura Opii et Glycyrrhizae Co</i> , N. F.) contains antimony and potassium tartrate, as well as Camphorated Tincture of opium, glycyrrhiza and ethyl nitrite	4 cc.	1 fl. dr.
2. Compound Syrup of Squill, N. F. (<i>Syrupus Scillae Compositus</i>)	2 cc.	½ fl. dr.
3. <i>Mistura Pectoralis</i> , N. F. (Stoke's Expectorant) contains ammonium carbonate, senega, squill	4 cc.	1 fl. dr.
4. Elixir of Terpin Hydrate and Codeine, N. F. (each dose contains ¼ gr. codeine)	4 cc.	1 fl. dr.
5. Compound Tincture of Benzoin used by inhalation from hot water		
6. Syrup of Ipecac	0.75 cc.	12 min.

C. DRUGS USED TO RELAX BRONCHIAL SPASM
IN ASTHMA

Several drugs, which have been described elsewhere in the text under their chief therapeutic uses, are employed to relieve the paroxysms of asthma. They include amyl nitrite, atropine sulfate, belladonna, stramonium, ephedrine, epinephrine, spirit of glyceryl nitrate, potassium iodide, and sodium iodide.

Oxygen and Oxygen Therapy

Oxygen is a gas which constitutes 20 per cent of ordinary air, and which is necessary to maintain life. Oxygen, U. S. P., is oxygen in a compressed state. It is colorless, odorless and tasteless gas. It is not inflammable but it supports combustion much more vigorously than does air.

Oxygen is compressed and marketed in steel cylinders which are fitted with reducing valves for the delivery of the gas. Because it

2. Pulmonary edema.
3. Severe asthma.
4. In cardiac failure or threatened cardiac decompensation and coronary occlusion.
5. In treatment of poisoning from carbon monoxide and other gases.
6. In anesthesia to increase the safety of general anesthetics.
7. In addition, oxygen is reported to have given very satisfactory results in the treatment of certain types of headache.
8. In the treatment of abdominal distention due to intestinal ileus.

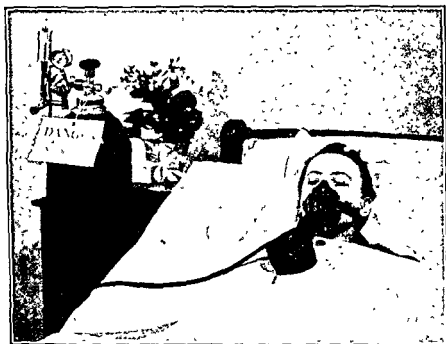


Fig. 24—An oronasal type of B.L.B. oxygen inhalation apparatus in place. The nurse must exercise care that the retaining strap is not on too tight. It is sufficiently tight if the reservoir-rebreathing bag is moving up and down regularly with each respiration. Any concentration of oxygen up to 100 per cent can be given with such an apparatus.

The gas causing gastrointestinal distention is mostly nitrogen. When the patient inhales pure oxygen or a very high concentration of oxygen, the nitrogen which is dissolved in the blood gradually leaves by way of the lungs. The blood is then able to absorb the nitrogen from body cavities, such as the intestine, discharge it into the expired air, and thus relieve distention and gas pain.

Administration of Oxygen.—Oxygen is administered in a number of ways including the oxygen tent, nasal catheter, face mask, head tent, and the oxygen chamber. The problem of administering gas in a concentration high enough to be beneficial without excessive

is changed relatively little. However, in conditions characterized by oxygen want, any increase in the oxygen content of the blood is certain to be beneficial. Inhalation of pure oxygen may bring about an increase of oxygen in the arterial blood to the extent of 15 per cent more than it usually carries. The beneficial effect is apparently due more to the increased oxygen pressure in the tissues than to the increased content of the blood. While a difference of opinion exists as to the effect of high concentrations of oxygen upon body tissues, especially those of the lungs, there seems to be a growing belief that pure oxygen may not have an injurious effect in the human lung, and that when conditions seem to warrant high concentrations they should be used.



Fig. 23.—Nasal type of B.L.B. oxygen inhalation apparatus in position. To keep the patient comfortable both the oronasal and the nasal type of apparatus should be removed at intervals of two hours, when the patient's face should be washed and the skin dried and powdered.

Purposes for Giving Oxygen.—Oxygen is used in medicine chiefly (1) to prevent and eliminate anoxemia, (2) to supply an increased demand for oxygen by the body cells, and (3) to decrease cardiac effort. It is indicated therefore in the following:

1. Pneumonia, both lobar and bronchopneumonia, to increase the oxygen content of the blood and to relieve cyanosis and dyspnea; to reduce high temperature and tachycardia.

It is recommended for status asthmaticus, bronchiectasis, emphysema, and for anesthesia when dealing with a respiratory tract in which there is obstruction of some form.

Questions for Review

1. Indicate two ways in which drugs affect the respirator system.
2. Name several conditions during which coughing may be extremely harmful to a patient.
3. How may drugs act so as to produce relief from a cough?
4. Name several drugs illustrating the systemic action
5. Define demulcent: give some examples.
6. How do expectorants produce their effects? In what conditions are they useful?
7. Under what conditions is it preferable to stimulate expectoration?
8. Why does increased humidity of atmosphere in itself help to relieve coughing?
9. Mention several points which are essential in good nursing for a patient who is receiving steam inhalations.
10. How can a nurse help to minimize waste and expense in the administration of oxygen and carbon dioxide?
11. Why must a nurse exercise caution when giving advice about the free use of nose drops, nasal sprays, etc.
12. What harmful effects may result from over medication of the nasal mucous membranes?
13. Give the dosage and method of administration of the following:

(a) Ammonium chloride	(d) Oil of eucalyptus
(b) Tartar emetic	(e) Potassium iodide
(c) Tincture of benzoin	
14. Give the action and uses of terpin hydrate
15. Name several drugs which may be used to relieve the spasms of asthma.
16. Name the common respiratory antiseptics. Discuss their value.
17. Give the therapeutic uses of oxygen.

waste has not been easy, especially when the oxygen tent is used. A concentration of approximately 50 per cent is usually ordered although higher concentrations are also used. The oxygen tent continues to be a favorite method of giving oxygen in many hospitals and for certain types of patients who are unable to tolerate a face mask. In the oxygen tent or room are special devices for regulating temperature and humidity. In caring for the patient the nurse must plan her care of the patient so that the tent is removed or opened as little as possible. In addition, she should keep in mind two of the important properties of oxygen: first, that oxygen supports combustion and that any combustible material will burn with much greater ease and intensity when the oxygen content of the atmosphere is increased over and above the normal content. Visitors must be carefully instructed and watched to prevent any form of fire from entering the room where oxygen is being given. Hand bells are used in preference to an electric call signal. The application of lights to the wound, the use of an electric cautery, and a hot plate for steam inhalations are further examples of situations to be avoided when there is a source of oxygen under pressure in the room.

Second, oxygen is heavier than air, and to prevent needless waste of oxygen a rubber sheet should cover the entire mattress and the canopy of the tent must be well tucked under the mattress and around the patient.

The mechanical simplicity and ease of operation make the face mask useful for oxygen administration in small hospitals, in the home, and also by pilots and passengers of airplanes. By this method oxygen of any desired concentration can be given economically and efficiently. Some patients, however, object to having the mask against the face for prolonged periods of time.

Helium

Helium-oxygen mixtures have been used for some time to treat obstructive types of dyspnea. Helium is an inert gas and so light that a mixture of 80 per cent helium and 20 per cent oxygen is only one-third as heavy as air.* Helium is only slightly soluble in body fluids and has a high rate of diffusion. Its low specific gravity makes it possible for mixtures of this gas with oxygen to be breathed with less effort than either oxygen or air alone when there is obstruction in the air passages

*Goodman, L., and Gilman, A. The Pharmacological Basis for Therapeutics, New York, 1941, The Macmillan Co., p. 690.

It is recommended for status asthmaticus, bronchiectasis, emphysema, and for anesthesia when dealing with a respiratory tract in which there is obstruction of some form.

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17. Give the therapeutic uses of oxygen.

UNIT VII

CHAPTER XVI

PHARMACOLOGY AS RELATED TO THE SKIN AND MUCOUS MEMBRANES

The skin is the largest organ of the body. It consists of two principal layers: (1) the epidermis, outer layer or cuticle, which is non-vascular, and (2) an inner layer of connective tissue containing blood vessels, nerves, and lymphatics. Four epidermal sublayers or strata are recognized as follows: (a) the stratum germinativum, the deepest layer where regeneration occurs; (b) the stratum granulosum, a thin layer of cells; (c) the stratum lucidum, also very thin and not visible unless the skin is thick; and (d) the stratum corneum, or outermost layer composed of flattened, dry, dead cells which gradually are exfoliated, as dandruff.

Functions of the Skin.—The skin (1) serves as mechanical protection for the underlying parts; (2) prevents the penetration of liquids and noxious gases; (3) protects against light (due to a pigment melanin) and heat rays; (4) aids in regulating the body temperature; (5) by reason of secretion of sweat and sebum, it is an excretory organ; (6) it is a metabolic organ (vitamin D is formed to some extent in the skin by the action of ultraviolet light on ergosterol), and (7) it is a sensory organ between the organism and its environment.

Absorption From the Skin.—Absorption from the skin is poor and uncertain. The lower layers of the skin absorb readily. The stratum corneum and thick layers absorb but little. Absorption is increased if the skin is macerated either by water or by perspiration. Absorption is greatest where the epidermis is thin, as in the axilla. Absorption from the skin of children may be rather rapid. Raw surfaces also absorb quite rapidly. The nature of the vehicle is also important. Alcohol and volatile solvents increase absorption. Methyl salicylate rubbed on the skin may be found in the urine in thirty minutes. Mercury in the form of an ointment is also absorbed. Drugs that are fat soluble may be absorbed more rapidly than water.

soluble drugs, and natural fats make a better ferry by which the drug is absorbed through the skin than substances such as petrolatum.

At best, however, absorption is rather uncertain when drugs are applied by inunction.

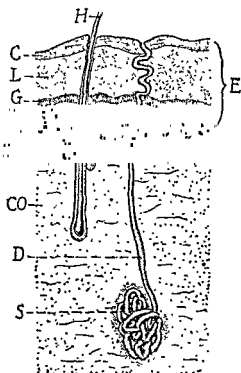


Fig. 25.—Magnified cross section of human skin. *E*, epidermis; *H*, hair; *S*, sweat gland; *D*, duct from sweat gland; *CO*, corium; *B*, basal layer of epi-

Excretion of Drugs Through the Skin

The amount of any excretion through the skin is difficult to investigate. Nitrogen loss through the skin may be determined by clothing the person in a nitrogen-free suit—cotton, washing it out after a time and determining the nitrogen chemically. The amount is very small. Drugs may be excreted to some extent by the skin—but the amount in any case is minimal. Silver, copper, arsenic, mercury, bromides, borates, phenol, salicylates, antipyrine, methylene blue, phenolphthalein may be deposited in the skin and sweat glands, and explain the exanthemas sometimes caused. A number of drugs like arsenic, selenium, iodides, bromides, phenolphthalein, quinine, etc., may cause skin eruptions. (See Figs. 26 and 27.)

Bromidrosis (Osmidrosis)

Bromidrosis is a disorder of sweat glands associated with disagreeable odor. It generally occurs where sweat is secreted in excessive amounts. The odor is supposed to be due to decomposition of the sweat after excretion. If the bromidrosis is localized, as in the feet, its cause is attributed to *Bacterium fetidum* of Thin, and ascribed to decomposition of the fatty acids of the sweat.



Fig. 26 —Bromide eruption due to taking a nerve sedative for insomnia (From Clendenning *Methods of Treatment*)

Therapeutics.—Absolute cleanliness. Bathing with antiseptic solutions such as 1:1000 solution of potassium permanganate; solution of cresol, 2 or 3 teaspoonfuls in a gallon of water; formalin 2 per cent solution or alum 1 per cent solution; the local application of aluminum chloride, 30 per cent or of urea 2 to 10 per cent. Ointments containing 2 per cent salicylic acid with 10 per cent boric acid and other antiseptic ointments may also be valuable. Some of the well-known deodorants on the market owe their efficacy to benzoic acid

and zinc oxide, zinc oxide alone, or boric acid. Deodorants which suppress the flow of perspiration usually contain aluminum chloride in varying degrees of strength.



Fig. 27.—Quinine eruption. (From Clendening: *Methods of Treatment*.)

Persons who are at first tolerant to a drug may, after using it for some time, become allergic. Such cases have occurred with quinine.

CLASSIFICATION OF DRUGS APPLIED TO SKIN AND MUCOUS MEMBRANE

1. Preparations which soothe
2. Antiseptics
3. Stimulants

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Preparations.—

White Ointment (Unguentum Album), U. S. P., a mixture of wool fat, white wax and white petrolatum.

Zinc Oxide Ointment (Unguentum Zinci Oxidi), U. S. P., contains 20 per cent zinc oxide in a base of wool fat and white ointment.

Zinc Stearate (Zinci Stearas), U. S. P., is a compound of zinc with variable proportions of stearic and palmitic acids. It contains about 14 per cent zinc oxide and is very similar to zinc oxide. Much used as a dusting powder.

Calamine Lotion (Lotio Calaminae), U. S. P., contains prepared calamine 8 parts, glycerin 2 parts, limewater to make 100. It is used as a soothing lotion on the skin.

Aluminum Subacetate, N. F. 2-5 per cent solution is used on compresses of sterile gauze which are kept continuously wet with the solution. It is used especially for first degree burns

Lime Liniment (Carron Oil), N. F., which is a mixture of linseed oil and limewater, is used for its soothing effect and to relieve pain in first degree burns. It is not antiseptic and may not be sterile

B. Antiseptics and Parasiticides

1. FOR DISEASE CONDITIONS OR INFESTATIONS OF THE SKIN.—Strong solutions of commonly used antiseptics such as bichloride of mercury, phenol, lysol, etc., are likely to be so injurious to the skin that they accomplish more harm than good. Preparations of sulfur and the mercurials lead in usefulness.

a. *Sulfur Ointment*, U. S. P., contains about 15 per cent of precipitated sulfur in a base of wool fat and white ointment. It is a valuable drug in the treatment of fungous growths (ringworm), scabies and seborrheic infections, as well as pediculosis. On the other hand, the use of too strong a preparation or the prolonged use of a sulfur ointment may give rise to skin irritation.

b. *Ammoniated Mercury Ointment*, U. S. P. This preparation contains 5 grams of ammoniated mercury in each 100 grams of finished preparation along with wool fat and white ointment. This preparation is of value in the treatment of streptococcic and staphylococcic infections of the skin.

c. *Potassium Permanganate* solution (1:4000) may be an effective antiseptic when used in this dilute form. It is sometimes prescribed for foot soaks for epidermophytosis of the feet.

d. *Balsam of Peru*, U. S. P., consists of a dark brown viscid liquid which may be used full strength or diluted with a vegetable oil. It is

4. Keratolytics
5. Antipruritics
6. Protectives
7. Astringents

A. Preparations Which Soothe

1. *Emollients* are fatty or oily substances which may be used to soften or soothe irritated skin and mucous membrane. An emollient may also serve as a vehicle for application of other medicinal substances.

2. Soothing preparations may also be liquids which carry an insoluble powder or suspension or they may be a mild acid or alkaline solution such as boric acid solution, limewater or aluminum subacetate. Zinc oxide, zinc carbonate (calamine), and the bismuth salts (subcarbonate and subnitrate), and starch are also commonly used for their soothing effect.

SPECIFIC PREPARATIONS.—

Benzoinated Lard, U. S. P., is made by incorporating 1 per cent of benzoin with lard and straining. The addition of the benzoin hinders the development of rancidity. It is used as an ingredient of ointments.

Hydrous Wool Fat, U. S. P. (Lanolin), is made by incorporating the purified fat of sheep's wool with 25 to 30 per cent of water. Hydrous wool fat is used as an ointment base. It does not become rancid, and as much as twice its weight of water can be incorporated with it. It has a somewhat unpleasant odor. It requires dilution for use in ointments and from 20 to 100 per cent of petrolatum may be added for this purpose.

Liquid Petrolatum is used as a vehicle for medicinal agents for local application. Light liquid petrolatum is employed as a spray.

Oil of Theobroma, U. S. P. (Cacao or Cocoa Butter), is a fixed oil expressed from the roasted seeds of *Theobroma cacao*. It is a yellowish white solid, having a faint, agreeable odor, and a bland chocolate-like taste. It is used chiefly for making suppositories, and to some extent as a lubricant in massage and as an application to sore nipples.

FIXED OILS—The fixed oils are also valuable as emollients. These include olive oil, obtained from the ripe fruit of the *Olea europaea*; the oil of linseed or flaxseed; and cottonseed oil, which is expressed from the seeds of the cotton plant.

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d. *Balsam of Peru*, U. S. P., consists of a dark brown viscid liquid which may be used full strength or diluted with a vegetable oil. It is

used in the treatment of epidermophytosis, pediculosis, scabies, and applied to dressings which cover wounds.

e. **Larkspur** and **kerosene** are also effective parasitocides for lice

f. **Dyes** such as **gentian violet** 1 per cent, **mercurochrome** 2 per cent, **acriflavine** 1:800, and **brilliant green** 2 per cent, are also effective antiseptics but their violent color makes them unsightly when applied to exposed parts of the body.

g. **Benzoic Acid**, U. S. P., can be safely applied to skin even in high concentration. As one of the substances found in **Whitfield's ointment**, it is used particularly for epidermophytosis of the feet.

Compound Ointment of Benzoic and Salicylic Acid, N. F. (**Whitfield's Ointment**), contains salicylic acid, benzoic acid, wool fat, and white petrolatum.

2. **FOR DISINFECTION OF THE SKIN.**—It is quite generally agreed upon that thorough washing of the skin with warm water and soap should precede the use of antiseptics on the skin. It is impossible to sterilize the skin, but adequate soaping and washing will do much to remove bacteria and the outer loose epithelium. Strong antiseptics may again do more harm than good by setting up an irritation which will decrease the natural resistance of the skin to bacterial invasion. Antiseptics which are used to lower the bacterial content are presented in Chapter X.

C. Stimulants and Irritants

Stimulants are those substances which produce a mild irritation and in that way promote healing and the disappearance of inflammatory exudates. Most of the irritant drugs when applied in low concentrations exert a stimulating effect. Good examples of preparations which may have a stimulant effect are the tars obtained from the destructive distillation of wood and coal.

Tars when diluted act as antiseptics as well as irritants. Official preparations include, **Pine Tar Ointment**, U. S. P.; **Pine Tar**, U. S. P.; **Juniper Tar**, U. S. P.; and **Coal Tar**, U. S. P. The tars are sometimes prescribed in the treatment of psoriasis and eczema dermatitis. The official tars are seldom employed full strength. Coal tar is the most antiseptic, but also the most irritant and has the most disagreeable odor.

Vulneraries are a form of tissue stimulant which is used to hasten the granulation of wounds or stimulate the growth of cells over a denuded area.

Cod-liver Oil Ointment has been found to have a slight bactericidal effect and to be one of the few stimulants of epithelial growth, which at the same time does not have an undesirable irritant effect.

Balsam of Peru, U. S. P., is a common vulnerary. It is a balsam obtained from the *Toluifera pereirae*, a tree of the West Indies, and occurs as a dark brown, syrupy liquid that does not harden on exposure to air. It contains resins and traces of cinnamic and benzoic acids. Balsam of Peru is applied in the form of the ointment, or in alcoholic solution, or mixed with castor oil.

The Compound Tincture of Benzoin, U. S. P., is useful as a stimulant and protective for ulcers, bed sores, cracked nipples, and fissures of the lips, anus, etc.

Preparations made of red blood cells have also been used to stimulate healing of indolent wounds and ulcers.

Irritants are agents which injure the skin and set up defense mechanisms which protect the tissues. The first response to local irritation is increased blood supply to the part, redness, and feeling of warmth. Drugs which when rubbed on the skin produce a hyperemia are called rubefacients. Turpentine, camphor, chloroform, ammonia, and methyl salicylate in the form of liniments all have a rubefacient action. Mustard and capsicum plasters are also rubefacient in effect, and if applied too long may act as vesicants.

Vesicants are irritants which are capable of greater irritation. They cause the capillaries to dilate widely and become permeable. This results in escape of plasma and the formation of blisters. Vesicants are little used today. Cantharides and ammonia are typical vesicant drugs. Many rubefacients are capable of acting as vesicants if used too strong or too long.

Escharotics, Corrosives, or Caustics are substances which cause necrosis or death of tissue. They act by combining with the tissue and precipitating it as a compound. The caustics are acids (glacial acetic or nitric), alkalies such as sodium or potassium hydroxide, metallic salts like silver nitrate or zinc chloride, or concentrated phenol. Carbon dioxide in either liquid or solid form is able to destroy tissue by freezing it. Corrosives or caustics are used to remove exuberant granulations, polypi, warts, and similar pathologic growths. They should not be used in the treatment of moles or precancerous skin conditions because of the danger of stimulating malignant degeneration.

D. Keratolytics

Keratolytics (horn dissolvers) are drugs which soften scales and loosen the outer horny layer of the skin. Salicylic acid, U. S. P., and resorcin (Resorcinol), U. S. P., are the drugs of choice. Their action makes possible the penetration of other medicinal substances by a cleaning of the lesions involved. Salicylic acid, U. S. P., is particularly important for its keratolytic effect in local treatment of scalp conditions, warts, corns, fungous infections, and certain types of dermatitis. It is used in ointments or in collodion up to 20 per cent for this purpose.

E. Antipruritics

Antipruritics are drugs given to allay itching of skin and mucous membranes. There is less need for these preparations as the constitutional treatment of patients with skin disorders is better understood. Dilute solutions containing phenol as well as tars have been widely used. They may be applied as lotions, pastes, or ointments. Dressings wet with potassium permanganate 1:4000 aluminum subacetate 1:16, boric acid, or normal saline may cool and soothe and thus prevent itching. Lotions such as calamine or calamine with phenol, cornstarch or oatmeal baths, as well as anesthetics like nupercaine, benzocaine, and holocaine may also be employed to relieve itching. It may also be necessary to administer sedatives which have a systemic effect; barbiturates, paraldehyde, or possibly bromides.

In addition to the above measures used to relieve itching, preparations of ergotamine are used to relieve the generalized itching associated with jaundice, cirrhosis of the liver, Hodgkin's Disease, etc. Ergotamine Tartrate, U. S. P. (Gynergen) is one of the preparations, and there are others, one of which is Dihydroergotamine (Sandoz). This preparation is said to relieve itching in a way similar to Gynergen without producing the common undesirable side effects of gynergen; i.e., nausea, vomiting, and cardiovascular reactions.

Other preparations to relieve itching related to allergic reactions are the antihistamine drugs (see p. 303).

F. Protectives

Protectives are soothing, cooling preparations which form a film on the skin. Protectives to be useful must not macerate the skin, must prevent drying of the tissues, and must keep out light, air, and dust. Nonabsorbable powders are usually listed as protectives, but

they are not particularly useful because they stick to wet surfaces and have to be scraped off and do not stick to dry surfaces at all.

Collodion, U. S. P., is a 4 per cent solution of pyroxylin, or gun-cotton, in a mixture of ether and alcohol. When collodion is applied to the skin, the ether and alcohol evaporate, leaving a transparent film which adheres to the skin and protects it.

Flexible Collodion, U. S. P., is a mixture of collodion with 2 per cent of camphor and 3 per cent of castor oil. The addition of the latter makes the resulting film elastic and more tenacious. *Styptic* collodion contains 20 per cent of tannic acid and is, therefore, astringent as well as protective.

Adhesive Plaster is a tenacious preparation solid at ordinary temperature but pliable and adhesive at the temperature of the body. It consists of rubber, lead plaster and vaseline spread on linen or muslin. Besides its use as a general protective agent, adhesive plaster is widely used to reenforce weak muscles, cover ulcers, limit effusions, etc., and to keep dressings in place.

Gelatin Preparation is a compound of gelatin mixed with zinc oxide, glycerin, and phenol. It may be used on dressings applied to chronic ulcers, abraded surfaces, and on the pressure bandages applied to varicose veins.

Surgical Paraffin.—This paraffin is a waxlike substance which is solid at room temperature but melts upon heating. It acts mechanically by coating the affected ulcer or surface with a thin film which excludes the air.

Nonabsorbable Powders include zinc stearate, zinc oxide, certain bismuth preparations, talcum powder, and aluminum silicate. The disadvantages associated with their use have been mentioned above.

G. Astringents

Astringents are drugs which tend to harden and contract tissues with which they come in contact. When applied to mucous membranes or to denuded or bleeding areas, they coagulate the albumins of the superficial layer of cells, thus hardening and contracting them. This action also forms a thin coating over the cells which protects them from irritation and promotes healing. They constrict the small blood vessels in the area of their application, thus relieving congestion; and they stop bleeding by coagulating the blood albumin at the point of rupture of the blood vessel.

Astringents may be divided into two groups: Mineral or Inorganic Astringents and Vegetable or Organic Astringents.

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tissue anoxia. Lack of sufficient oxygen and the accumulation of waste products resulting from inadequate oxidation result in loss of tone in the minute blood vessels and the increased capillary permeability then extends to tissues remote from those suffering the initial injury. Thus a generalized edema often develops and the vicious cycle once established tends to be self-perpetuating. One of the aims in the treatment of burns is therefore to stop the loss of plasma in so far as possible and replenish that which is lost as quickly as possible.

Second or third degree burns must be thought of as open wounds with the accompanying danger of infection. Another aim must be to prevent or treat infection. The treatment, however, must be such that it will not bring about any further destruction of tissue or the small islands of remaining epithelium from which growth and regeneration can take place. In addition, the sick tissues must be placed at rest to facilitate the healing powers of nature.

Local Treatment.—Sometimes the best local first aid treatment is to cover the burned area with as clean a towel or dressing as may be obtained until the part can be treated aseptically in a hospital. The first impulse of many well-intentioned persons to apply some greasy ointment such as lard or butter is often a bad one, for such a measure may be the means of infecting the wound. Furthermore, the chances are that all of the grease or ointment will have to be removed later if the burn is anything more than a superficial first degree burn.

If the burned area is contaminated, it is usually necessary to cleanse it. This may be done by washing it gently with water and a simple white soap (never tincture of green soap) or by irrigation with warm isotonic salt solution. The cleansing must be done gently with a minimum of trauma and with the surgical cleanliness routine as employed in an operating room.

After the burned surface has been cleansed and loose tissue removed, the wound must necessarily be covered. Some physicians are using a nonadherent dressing which will permit free drainage but can be removed with a minimum of difficulty. The dressing is usually of gauze and may be impregnated with a number of different sterile ointments such as petrolatum, zinc peroxide, xeroform, sulfathiazole, or sulfadiazine. It is important that the dressing be simple and nonirritating. Over the nonadherent dressing a compression dressing made of gauze and mechanic's waste, or some similar material, may be applied and bandaged firmly and securely in place. The compression dressing serves to prevent further fluid

The mineral astringents are various salts of metals, the most important of which are the following:

Alum	Potassium Chlorate
Bismuth Subnitrate	Silver Nitrate
Bismuth Subcarbonate	Zinc Acetate
Ferric Chloride	Zinc Chloride
Lead Acetate	Zinc Sulfate
	Zinc Oxide

Vegetable astringents are vegetable substances which owe their power to contract tissues to the tannic acid which they contain. Tannic acid is used externally as an astringent and hemostatic, and internally to check diarrhea. Solutions of 5 to 20 per cent are used on inflamed mucous membranes, especially in pharyngitis, and solutions of from $2\frac{1}{2}$ to 5 per cent are applied or sprayed on burns. It is also employed locally in the treatment of hemorrhoids in the form of a 20 per cent ointment or a suppository containing 0.1 Gm. ($1\frac{1}{2}$ grains). A very important use of tannic acid is as an antidote to various alkaloids and metal poisons. As tea leaves contain considerable tannic acid, they are usually the most convenient source of this antidote in an emergency.

Glycerite of Tannic Acid, U. S. P., is a 20 per cent solution of tannic acid in glycerin. It affords a convenient means for making dilute solutions for local use.

Burns

The problems associated with the treatment of burns have been increased by the numbers of burned patients returning from the theatres of war as well as the increasing numbers of such patients from civilian life. It is said that approximately 6000 people die each year of burns in the United States alone. The chief cause of death is shock, a fact of considerable significance in any effective plan of treatment.

Consideration of what takes place in the damaged tissues clarifies many points of treatment. At first there is an altered capillary permeability in the local injured area. That is, the permeability is increased and a loss of plasma and weeping of the surface tissues result. If the burn is at all extensive, considerable amounts of plasma fluid may be lost in a relatively short time. This depletes the blood volume and causes a decreased cardiac output and diminished blood flow. Unless the situation is rapidly brought under control, irreparable damage may result from the rapidly developing

epithelium may be destroyed and thus healing is delayed. (4) Tanning with tannic acid frequently leads to unsatisfactory cosmetic results. Some authorities are of the opinion that tannic acid and silver nitrate preparations are useful because they dry more quickly than tannic acid alone and thus less tannic acid is absorbed into the general circulation. It is conceded that tannic acid has no doubt saved many lives because it has been one means of closing the wounds and preventing loss of plasma from the surface but apparently it has little effect in preventing the loss of fluid into the deeper and more remote tissues. It also is effective in helping to relieve pain, and it may delay the development of infection in the third degree burn and definitely helps to prevent infection in the second degree burn.

General Treatment.—

a. *Analgesics*.—Since pain does intensify the shock associated with burns, its control is important. Morphine continues to be the analgesic of choice. Intravenous administration is advised when the absorption from subcutaneous tissues promises to be poor or unreliable because of the inadequacy of circulation. Large doses are to be avoided because of the danger of respiratory depression and because large doses in some instances do not relieve pain better than moderate doses. The dosage recommended for intravenous administration is 0.008-0.011 Gm. ($\frac{1}{8}$ - $\frac{1}{6}$ gr.).

b. *Sedatives*.—States of fear and hysteria are best relieved by one of the barbiturates. Pentobarbital is a good choice. Its sodium salt may be given intravenously if necessary (gr. $1\frac{1}{2}$).

c. *Measures to Relieve Shock Due to Loss of Heat*.—Heat should be provided in moderation. Room temperature should be about 75° F. Although the feet of the patient suffering from shock may be cold, it is thought to be unwise to interfere with Nature's way of trying to conserve blood volume for the vital parts of the body by trying to warm up the patient's extremities.

d. *Measures to Relieve Shock Due to Loss of Plasma*.—It has been suggested that for every 10 per cent of body surface burned a pint of blood plasma should be given.¹ In other words plasma administration is on a quantitative basis, and the total amount required will also depend upon the individual patient. The giving of plasma may be the measure which should be instituted before all others. Other treatment may be useless if the patient is allowed to sink into a circulatory collapse. Oxygen may be indicated in severe cases. If hemorrhage has accompanied the loss of plasma, blood transfusions may also be

loss from the tissues. It is then thought advisable to put the part at rest and not disturb the dressing any more than absolutely necessary.

Other authorities recommend a local treatment of burns which involves the use of a paraffin wax spray and no dressing. The paraffin wax formula* includes the following:

Paraffin wax -----	670 Gm.
Household wax, melting point about 125° F. This softens the skin. For first aid ointment reduce to only 20 Gm. rather than 670 Gm.	
Petrolatum -----	250 Gm.
Liquid Petrolatum (heavy) -----	150 cc.
Cod Liver Oil -----	50 cc.
Cotton seed oil or olive oil has been substituted satisfactorily	
Sulfanilamide powder -----	50 Gm.
Resorcinol 10 Gm. in 15 cc. of ethyl alcohol has been used as an effective antiseptic (before sulfanilamide)	
Menthol -----	1 Gm.
Camphor -----	1 Gm.
These relieve burning or itching sensations	
Oil of Eucalyptus -----	1 cc.
Used as a deodorant	

The above mixture is sprayed on all burned areas either immediately or just after the application of sulfanilamide powder. It may be sprayed upon the burned surfaces as often as necessary for the first few days and then once daily or oftener thereafter. Some of the advantages claimed for the use of the paraffin wax treatment are that there is no trauma and injury from the cleansing or use of tanning agents, chemical irritants, or frequent dressings; it relieves pain effectively; it is applicable to any part of the body; it is inexpensive, it allows for free movement; and wounds are easily inspected.

Although tannic acid is still used by some physicians, especially over areas other than the face and hands, it is rapidly giving way to other forms of treatment. A number of reasons are offered to explain its decreasing popularity. (1) The absorption of tannic acid may lead to liver necrosis. (2) The brittle eschar may crack and then the third degree burns are easily infected, especially in the more mobile areas of the body. (3) Difficulty in removing the eschar is sometimes experienced, and as a result the small islands of

*Pendleton, R. C.: J. A. M. A. 122: 415, June 12, 1943.

epithelium may be destroyed and thus healing is delayed. (4) Tanning with tannic acid frequently leads to unsatisfactory cosmetic results. Some authorities are of the opinion that tannic acid and silver nitrate preparations are useful because they dry more quickly than tannic acid alone and thus less tannic acid is absorbed into the general circulation. It is conceded that tannic acid has no doubt saved many lives because it has been one means of closing the wounds and preventing loss of plasma from the surface but apparently it has little effect in preventing the loss of fluid into the deeper and more remote tissues. It also is effective in helping to relieve pain, and it may delay the development of infection in the third degree burn and definitely helps to prevent infection in the second degree burn.

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necessary. Fluids such as normal saline or 5 per cent glucose should be given in quantity sufficient to insure a urinary output of 1200-1500 cc. of urine. Late control of anemia and malnutrition also includes transfusions of whole blood, proteins, or amino acids.

e. Prevention and Treatment of Infection.—Chemotherapy is advocated for all burn patients except those having first degree burns or those with burns of small extent in which the epidermis is intact. Both the sulfonamide drugs and penicillin are of value. Sulfadiazine seems to be the sulfonamide of choice. The sodium salt may be given intravenously, and the blood level of between 6 and 12 mg. per 100 cc. of blood is recommended.*

The blood level is more easily controlled when the drug is administered intravenously than when it is given in the form of ointments. Penicillin seems to be of great value, particularly against microorganisms not controlled by the sulfonamides.

Gentian violet and other dyes have been used locally but when present in bacteriostatic concentration, they appear to be toxic to tissues and may thus delay healing.

Tetanus toxoid or antitoxin may be administered to prevent the development of tetanus. Transfusions of whole blood are needed for severely burned patients whose wounds have become infected.

Sunburn

Sunburn is an acute erythema caused by too long an exposure to the rays of the sun. In some cases, especially if a large area is involved, it may be serious, and the skin surface should be treated as any serious burn. Exposure to the sun is preferably done gradually a few minutes each day when a general tan is desired. As would be true for any first degree burn when the epithelium is intact and remains so, ordinary protective demulcents or emollients are sufficient to allay irritation. A good cold cream (*unguentum aquae rosae*), mucilage of acacia, or olive oil may be used.

Butesin Picrate, N. N. R., is both antiseptic and anesthetic and is used in a 1 per cent ointment for burns. It is useful to relieve the pain.

HAIR DYE AND FUR POISONING

Cosmetic preparations are often toxic. Hair dyes often contain paraphenylenediamine, $C_6H_4(NH_2)_2$, which is quite toxic. It is also used for dyeing furs brown or black. Among the symptoms produced by it are dermatitis, lacrimation, asthenia, gastritis, vertigo, asthma.

*J. A. M. A., 125: 542, June 24, 1944

Industrial workers where this dye is used suffer mainly from eczema and asthma.

Cosmetics may also contain lead salts, silver salts, etc., which are not without danger. Depilatories, such as sodium and calcium sulfides, may produce irritation and dermatitis, especially if left on too long.

TESTS FOR HYPERSENSITIVITY—ALLERGIC REACTIONS

Some allergic reactions are distinctly pharmacologic and among others—skin reactions are manifest. The reactions appear analogous to the precipitation of protein. Skin tests for hypersensitivity are much used. The specific reactions of the skin to local inoculation are of two types: (1) the urticarial reactions produced by histamine, peptone, pollens, etc., to which the person is susceptible; (2) those indicating the presence of a specific infection, like the reaction to tuberculin. The skin reactions are a reliable qualitative but not quantitative index of hypersusceptibility.

When a patient is susceptible to certain proteins, etc., the application of a minute amount to a scratch on the skin, or the intradermal injection of a dilute solution produces a marked reaction manifested by a red spot or by a wheal similar to those which occur in hives. Patients suffering from hay fever may react to the causative agent, which may be the pollen of some plant like golden rod or timothy. Similarly, patients with asthma may react to animal hairs or dandruff, or food products, such as strawberries, eggs or milk. In many cases it is difficult or impossible to find the causative agent.

Baths

Baths may be employed to cleanse the skin, to medicate it, or to reduce temperature. The usual method of cleansing the skin is by the use of soap and water, but this may not be tolerated in skin diseases. In some cases even water is not tolerated and inert oils must be substituted. Persons with dry skin should bathe less frequently than those with oily skin. It is possible to keep the skin clean without a daily bath. Nurses are sometimes accused of over-bathing hospital patients, causing the patient's skin to become dry and itchy. An oily lotion is preferable to alcohol for the dry skin.

To render baths soothing in irritative conditions, bran, starch, gelatin, etc., may be added in the proportion of about 1 to 2 ounces to the gallon.

Soaps

Ordinary soap is the sodium salt of palmitic, oleic, or stearic acids or mixtures of these. They are prepared by saponifying fats or oils with the alkalis. The fats or oils that are used vary considerably. The oil used for castile soap is supposed to be olive oil. Some soaps are made with cocoanut oil to which skins of some persons are sensitive. Soaps contain glycerin unless it has been removed from the preparation. The consistency of the soap depends upon the predominating acid and alkali that is used.

Although all soaps are alkaline the presence of an excess of free alkali or acid will constitute a potential source of skin irritation. The best soaps are only slightly alkaline, and they are likely to be found among the most inexpensive soaps rather than in the highly scented, highly colored, and expensive varieties.

Medicated soaps contain antiseptics and other added substances, such as cresol, thymol, sulfur, etc.; but soaps per se are antiseptic only in so far as they favor the mechanical cleansing of the skin.

The belief that soap and water is bad for the complexion is erroneous for the most part. A clean skin helps to promote a healthy skin. The soap used in maintaining a clean skin should be mild and contain a minimum of irritating materials.

Soaps are irritant to mucous membranes, and their use in enemas is due mainly to this action. They are used in the manufacture of pills, liniments, and tooth powders. If soaps contain much free alkali their use on the skin may cause eczema.

Suggestions for Study and Review

1. Explain how the structure of the skin is related to its various functions?
2. If a drug is to be administered by inunction, what sites of the body *skin* surface would you choose for the treatment and why?
3. Why is disinfection of the skin surface practically impossible? Why is an attempt to disinfect the operative field always made?
4. What disinfectants for the skin are used in your hospital? What advantages and what disadvantages do they have?
5. Why is an extensive burn of the skin likely to be very dangerous? What are the main points of treatment? What is the most popular method for treatment of burns in your hospital?
6. Why must the nurse be especially careful not to give offense by bromidrosis? How may the eating of onion or garlic offend other than by causing unpleasant breath?
7. What type of advice may the nurse safely give to a person who complains of a dry, somewhat itchy skin?
8. Why is some of the current advertising of medicinal soaps likely to cause people to draw erroneous conclusions?

9. Why may cosmetic preparations cause manifestations of skin disease in some people? Why is the value of any cosmetic preparation definitely limited?
10. What is a liniment? How should it be administered?
11. Why is the administration of some drugs likely to be accompanied by disorders of the skin? What are some drugs which have such an effect?

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by intercellular substance. Elsewhere the capsule is lined by a layer of flattened cells. The capsule is connected to the tubule proper by a neck called the first convoluted tubule. The part is succeeded by a very tortuous proximal convoluted portion, which is continued toward the pelvis of the kidney as the descending limb of the medullary or Henle's loop, lined by flattened cells. This is followed by the ascending limb, which is lined by cubical cells, and then the distal convoluted portion, also lined by cubical cells. The convoluted portion empties into the collecting tubules which are lined by cubical cells. The collecting tubules lead into the termination of the renal tubule, and are lined by clear columnar cells. The loops of Henle and the collecting tubules

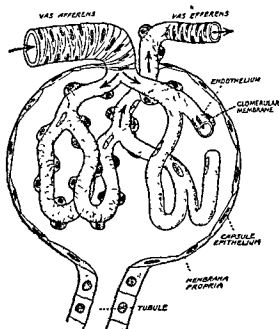


Fig. 23.—Diagram of a Malpighian body. This consists of a tuft of capillaries, the glomerulus, within an invaginated membrane, Bowman's capsule, which forms the head of the tubule. Note that the capsule epithelium is reflected over the outside of the capillaries of the glomerular tuft. There are in reality many more capillary loops than are shown. Blood enters the glomerulus from the *vas afferens*, and leaves it by the *vas efferens*. The former is definitely larger than the latter. (After v. Möllendorff from Winton and Bayliss: *Human Physiology*, ed. 2, London, 1935, J. & A. Churchill, Ltd.)

and the ducts of Bellini lie in the medulla of the kidney. The other parts of the tubule are found in the cortex. The number of glomeruli in the kidney, based on experimental evidence and counting, is estimated in one kidney as follows:

Rabbit	160,000-212,000
Dog	142,000
Sheep	505,000
Pig	700,000
Ox	4,025,000

Among the different species studied, it has been estimated that the number of glomeruli in both kidneys varied from 1,300,000 to 3,100,000 per square meter of body surface.

UNIT VIII

CHAPTER XVII

PHARMACOLOGY AS RELATED TO THE URINARY SYSTEM

Functions of the Kidneys

The kidneys are the chief organs that excrete nonvolatile water-soluble substances from the body. These substances are the end products of metabolism, which consist principally of urea, uric acid, organic salts, and foreign substances that may have gained entrance into the blood.

The normal kidney is impervious to the colloids, such as blood proteins, or to colloids introduced into the blood stream, such as gelatin or gum acacia. The kidney plays an important part in maintaining the osmotic pressure of the blood. It acts to maintain optimum concentrations of the individual constituents of the plasma. This is effected chiefly by the excretion of water, and by the secretion of blood constituents when they exceed the *threshold* concentration. The substances in the blood can be grouped into *threshold* and *no threshold*. Threshold substances are those like glucose, sodium chloride and bicarbonate, amino acids, etc., which must reach a certain concentration before they are excreted. Creatinine, sulfates, and foreign substances are excreted readily in any concentration and hence are designated *no threshold substances*. Between no threshold and threshold are medium-threshold substances that are excreted in increasing amounts in direct relation to their concentration in the blood. The no-threshold group includes potassium salts, phosphates, urea, and perhaps urates. Bile pigments, abnormal products of metabolism, such as β -hydroxybutyric acid, aceto-acetic acid, hematoporphyrin, and homogentisic acid (alkaptone).

Histology of the Kidney

The kidney is composed of many functional units termed *renal* or *urinary tubules*, each of which begins as a peculiar structure known as the *glomerular* or *Bowman's capsule*. Into Bowman's capsule is invaginated a tuft of capillary vessels, the glomerulus, from the renal artery. The capsule when it is reflected over the glomerulus is lined by a syncytium, i.e., cells which may be connected

in governing the amount of urine excreted. It may be assumed that on passage through the tubules some of the secreted water is re-absorbed, just as it would be on passage through the intestine. Diuretics, then, may act to some degree by preventing absorption from the tubules, similar to cathartics in preventing absorption from the intestines.

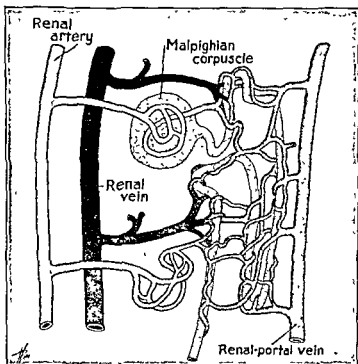


Fig. 29.—Diagram of blood supply of Malpighian corpuscle and of convoluted tubules in amphibian kidney. (Redrawn from Cushny.) The discoverer of these corpuscles was Marcello Malpighi (1628-1694), an Italian anatomist.

DIURETICS

Diuretics are drugs which increase the flow of urine. They produce this effect either by:

1. Stimulating the secreting cells in the kidney to greater activity; increasing the number of active glomeruli.
2. Increasing the circulation through the kidneys so that there is more blood from which to secrete urine or
3. Increasing the water content of the blood through osmosis or salt action.
4. Depressing the action of the tubule cells.

The following diuretics are not necessarily discussed in the above order.

Blood Supply of the Kidney

The blood supply of the kidney is derived from branches of the renal artery. All the blood supply reaching the capillaries of the different parts of the tubule must first pass through the capillaries of the glomerulus. The blood from the second set of capillaries is drained into the renal vein. The number of capillaries open and functioning at any one instant varies widely, and is never 100 per cent (Richards and Schmidt). The number may be increased by drugs that produce diuresis, such as glucose and caffeine, and decreased by adrenalin and pituitrin, which cause less urinary secretion. The number of open capillaries in a given glomerulus may also vary, and the blood flow may shift from glomerulus to glomerulus

Secretion of Urine

Five factors seem to control the secretion of urine. These are: (1) the blood pressure, (2) the presence of free water in the blood, (3) the amount of blood circulating through the kidneys, (4) the condition of functioning of the glomeruli, and (5) the absorption of water-soluble salts from the tubules.

1. To secrete urine the blood pressure must be 40 mm. of mercury or over. Little if any is secreted below this pressure.

2. Most of the water in the blood seems to be in a colloidal or combined form. Apparently only free water is secreted. In diseased conditions more than the normal amount may be combined, due to retention of salts or the effect of toxins, acidosis, etc. Purine preparations, salts, etc., may change the condition of the water-protein combination and also act on the secreting mechanism of the kidney.

3. The amount of blood flowing through the kidneys may be increased by cutting or depressing the vasoconstrictors from the renal plexus or by stimulating the vasodilators which are derived from the eleventh, twelfth, and thirteenth thoracic spinal nerves or by drugs which act to dilate the vessels. While the nervous mechanism profoundly affects the excretion of urine, the influence seems indirect, since adequate renal function can be maintained after all nerves are cut, and even after the kidneys have been removed and replaced.

5. Since apparently more water passes through the glomeruli than is excreted, absorption from the tubules seems an important factor

in governing the amount of urine excreted. It may be assumed that on passage through the tubules some of the secreted water is re-absorbed, just as it would be on passage through the intestine. Diuretics, then, may act to some degree by preventing absorption from the tubules, similar to cathartics in preventing absorption from the intestines.

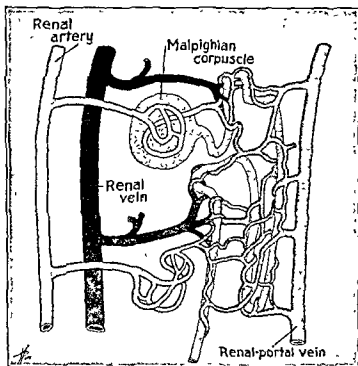


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The following diuretics are not necessarily discussed in the above order.

I. Water

Water is a diuretic in itself although seldom considered as a drug. Fluids are frequently forced to increase the urine output. The mechanism of water diuresis has been explained on the basis of decreased tubular reabsorption in the kidney. The activity of the tubule cells appears to be related to the concentration of the posterior pituitary secretion in the blood. When the fluid intake is increased, the pituitary principle is diluted, the activity of the tubule cells is decreased, and diuresis results.* Water is not a diuretic in the sense that it causes the excretion of edematous fluid from the tissues.

II. Saline Diuretics

A. **Sodium Chloride** may be administered for its diuretic effect in the form of either an isotonic or hypertonic solution.

Isotonic salt increases the volume of the extracellular fluids much more than plain water because its retention in extracellular fluids prevents passage of water into the cells due to the osmotic condition which has been established, i.e., equal salt concentration on both sides of the cell membrane. The blood volume is therefore increased which in turn promotes greater glomerular filtration. Tubular activity is not greatly altered and diuresis is slow but rather prolonged.

Hypertonic sodium chloride increases the blood volume by the amount of fluid injected and also draws fluid from the body cells. As a result the glomerular filtration is increased and, in addition, tubular reabsorption is decreased. The amount of sodium chloride in the glomerular filtrate limits the amount of reabsorption, and the kidney is forced to use a certain amount of fluid to excrete the excess sodium chloride. Hypertonic solutions of sodium chloride therefore exert a more powerful diuretic action than plain water or isotonic salt solution. The use of salt solutions would obviously be contraindicated in cases of clinical edema.

B. **Potassium Salts.**—When kidney function is normal, potassium ions are eliminated very rapidly. They are filtered by the glomerulus but rejected by the tubule and because there is a definite limit to the ability of the kidney to concentrate electrolytes, a certain amount of water must accompany the excretion of potassium.

Potassium Chloride, U. S. P., and Potassium Nitrate, N. F., are the preparations most commonly used, although the bicarbonate, citrate, and acetate salts of potassium are also used. The official

*Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 628.

dosage is 1 Gm. daily given orally in divided doses either during or just after meals. However, doses of 5-10 Gm. daily are not unusual. Enteric coated tablets or capsules lessen gastric irritation.

C. Acid-Forming Salts.—The acidifying diuretics are chiefly ammonium chloride, ammonium nitrate, and calcium chloride. These salts bring about a disturbance in blood chemistry to the extent that an acidosis results. The kidney, in its effort to maintain a constancy of body fluids, excretes the acid-forming radicals and inhibits tubular reabsorption.

Ammonium Chloride, U. S. P. The most convenient way of administering this salt is in enteric coated tablets or capsules. The amount varies but doses of 8-12 grams have been recommended. In many instances the salt must be given for several days. It should not be given when renal function is impaired because there is a danger of producing an uncompensated acidosis.¹

Ammonium Nitrate is not an official salt. Although it is soluble and produces the least amount of gastric distress, it sometimes gives rise to methemoglobinemia. Daily dosage of 12 grams in enteric coated preparations is recommended.²

Calcium Chloride, U. S. P., may be given either by mouth or intravenously, but it should never be given by injection directly into tissues because it is very irritating. Five to ten per cent solutions are used intravenously, but the injection should be made very slowly. Oral preparations are preferably given in enteric coated pills or capsules.

III. Hypertonic Solutions of Glucose and Sucrose

Glucose when given in quantity sufficient to exceed the renal threshold for this substance is not reabsorbed in the proximal tubule of the kidney and exerts osmotic changes in the more distal portion of the tubule resulting in increased excretion of water. To bring about this effect, however, the glucose concentration in the blood must be changed suddenly so that appreciable amounts are brought to the kidney within a short time. Hence the avenue of administration must be intravenous. The usual dose is 50 cc. of a 50 per cent solution.

Sucrose solution is likewise employed as an osmotic diuretic, and in some ways is more efficient than glucose. When given intravenously its form is too complex to be utilized by the tissues and

¹Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 631.

²Davison, F. R.: *Synopsis of Materia Medica, Toxicology, and Pharmacology*, St. Louis, 1944, The C. V. Mosby Co., p. 494.

the kidney excretes it as a foreign substance with little or no reabsorption in the tubule. It exerts osmotic effects similar to those of glucose. Since so very little is reabsorbed in the tubule, its effects are more lasting and dependable than those of glucose. The usual dose is approximately 100 cc. of a 50 per cent solution.

Large or repeated doses of these sugars are not advised because of the possibility of renal damage. Obviously they are contraindicated in patients with kidney disease. Glucose and sucrose are official and are marketed in sterile aqueous solutions up to 50 per cent concentration in ampules. They are used especially for treatment of cerebral edema and shock.

IV. Xanthine Diuretics

This group includes caffeine, theobromine, and theophylline, all of which are somewhat similar in action but vary in degree of action upon the various body structures. The body organs most affected by the xanthines are: (1) the central nervous system, (2) the kidneys, (3) cardiac muscle, (4) smooth muscle of the blood vessels, particularly the coronary vessels, and (5) skeletal muscle.

Caffeine exerts a marked action upon the nervous system but is relatively weak in its action upon the kidney, while theobromine and theophylline are weak in their action on the nervous system but have a definite action in the kidney and cardiovascular system.

The action of this group of drugs on the nervous system and on the heart and blood vessels has been discussed in previous chapters pertaining to these systems.

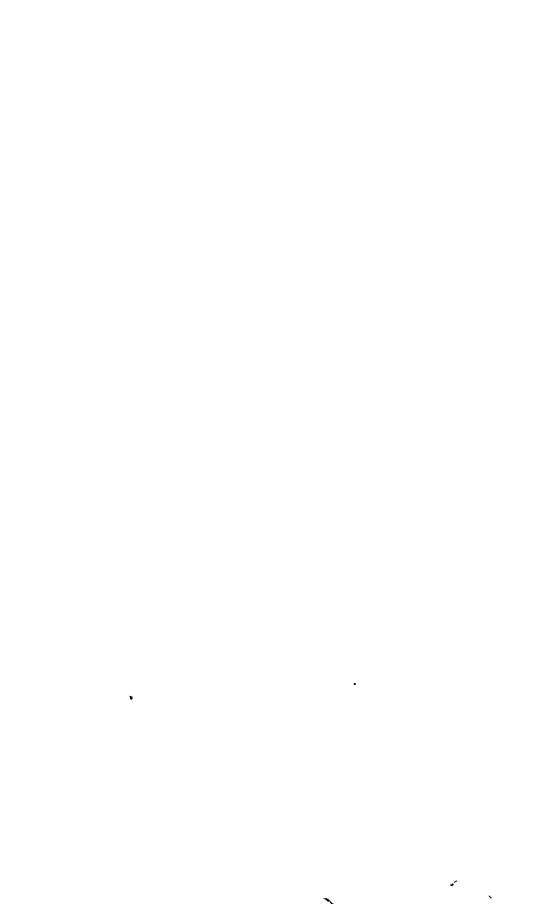
Theophylline is the more powerful diuretic, but its action is of short duration. Theobromine is somewhat less active but of longer duration. The mechanism of their diuretic action is somewhat obscure and subject of controversy. There appears to be evidence that they increase the number of functioning glomeruli in the kidney; that they increase the permeability of the cells of the glomerular capsule, and that they cause diminished absorption of water in the renal tubules.* Experiments seem to bear out the last-mentioned type of action particularly well.

Uses.—The xanthines are little used as diuretics unless edema is present. They are among the milder diuretic agents and satisfactory results are sometimes obtained when poor renal functions prevent the use of other diuretics. Caffeine is rarely employed for its

*Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 637.



PLATE XIII.—*Theobroma cacao* (Chocolate tree). (From Jackson. *Experimental Pharmacology and Materia Medica*.)



diuretic effect because of its weak action and its effect on the nervous system. For other uses see p. 300.

Theobromine is an alkaloid obtained from the seeds of the South American chocolate tree or *Theobroma cacao*. It is closely related, chemically, to caffeine. It occurs as a white, crystalline powder, having no odor and a bitter taste. It is very slightly soluble in water and consequently is used in the form of the freely soluble double salts.

Preparations

Theobromine and Sodium Acetate (*Theobrominae et Sodii Acetas*), U. S. P. (Agurin). Dosage: 0.5 Gm. (7½ gr.) orally.

Theobromine with Sodium Salicylate (*Theobromina cum Sodii Salicylate*), N. F. (Diuretin). Dosage: 0.5 Gm. (7½ gr.) orally.

Theocalcin, N. N. R. A double salt or mixture of calcium theobromine.

Theocalcin acts like theobromine but it is more soluble.

Theophylline, U. S. P. (*Theocin*), is the active principle of tea leaves but for commercial purposes it is produced synthetically. It is a white, crystalline powder, having no odor and a bitter taste. Theophylline is used as a diuretic in cardiac diseases, edema, nephritis, etc. It is similar in action to theobromine but is more active and often more effective. Its diuretic action ceases, however, after two or three days, and it is necessary to replace it by theobromine. Theophylline may cause irritation of the stomach and kidneys. The dose of theophylline is 0.2 and 0.3 Gm. (3 to 5 grains) three times a day.

Other Preparations.—

Aminophylline, U. S. P. (*Theophylline Ethylenediamine*). This preparation is readily soluble in water and may be given parenterally as well as by mouth. Aminophylline acts directly on the bronchial musculature to relax it when it is in spasm and for this reason is used for relief of bronchial asthma. It is also given for its diuretic effect in cardiorenal disease. Average dose: Oral, 0.2 Gm. (3 gr.); intramuscular or intravenous, 0.25 Gm. (4 gr.).

Theophylline and Sodium Acetate (*Theophyllina et Sodii Acetas*), U. S. P. This preparation is similar to theophylline but is more soluble. Dosage: 0.2 Gm. (3 gr.) orally or hypodermically.

Theophylline, U. S. P. Average dose: 0.2 Gm (3 gr.).

V. Mercurial Diuretics

The mercurial diuretics act upon the kidney itself and depress the cells of the tubules, thus preventing reabsorption of water.* Be-

*Bastedo, W. A.: *Materia Medica, Pharmacology and Therapeutics*, Philadelphia, 1938, W. B. Saunders Co., p. 609

cause of their irritant effects they are contraindicated in inflammatory conditions of the kidney. They are reputed to be the most powerful of any of the diuretic drugs and are especially useful to relieve edema due to congestive heart failure and in nephrosis. Favorable results have been reported for their use in ascites due to cirrhosis of the liver. The mercurials may be given alone or preceded by large doses of acidifying salts such as ammonium chloride or ammonium nitrate 4-10 Gm. (60-150 gr.).

Preparations and Dosage.—

Mersalyl, U. S. P. (Salysgan), is a complex synthetic drug containing 39.6 per cent of mercury. It is an odorless white crystalline powder, having a bitter taste. It is freely soluble in water.

Mersalyl is administered intramuscularly or intravenously in 10 per cent solution. An initial dose of 0.5 cc. (7 minims) is given to test the tolerance of the patient for mercury after which the dose is increased sufficiently to produce diuresis. The maximum dose is 2.0 cc. (30 minims). Injections are made at intervals of three to five days.

It is used especially in edema or ascites of cardiac origin. Profuse diuresis may follow a single injection.

Mersalyl and Theophylline Injection (Injectio Mersalyli et Theophyllinae), U. S. P. This preparation is a solution of 10 per cent mersalyl and 5 per cent theophylline. It combines the activity of a mercurial with that of a xanthine. It is said to be more effective than either drug alone, and less local reaction occurs from the combination than from mersalyl alone. Dosage: 2 cc. (30 minims) intramuscularly.

Mercurin is a complex organic mercurial which contains about 39 per cent of mercury. It is made up in suppositories which contain 0.5 Gm. of the drug mixed with cocoa butter. The dose is one suppository given rectally.

Mercurophylline Injection (Injectio Mercurophyllinae), U. S. P. (Mercupurin). This preparation is made up of mercurin and theophylline in chemical combination supposedly. It is marketed in ampules containing 1 or 2 cc. of the solution. When given intramuscularly the theophylline is thought to hasten absorption. It may also be given intravenously.

Symptoms of Mercurial Poisoning.—The signs of toxic reactions are the same as for other mercurials. Stomatitis, gingivitis, increased salivation, diarrhea, albuminuria, hematuria, and circulatory collapse. Mersalyl is said to be the least toxic.

Contraindications.—The mercurial diuretics are contraindicated in patients with acute nephritis, arteriosclerosis, or marked dehydration. Caution should be observed in administering the drug to patients with heart disease because of the danger of suddenly increasing the blood volume.

VI. The Circulatory Diuretics

Digitalis, strophanthus, and related drugs may cause diuresis in patients who have failing circulation, i.e., venous congestion, edema, and low arterial pressure. The edema is removed by improving the general circulation. The excess fluid is taken into the blood stream and disposed of in the kidneys. These drugs have no diuretic effect if the circulation is normal.

MEASURES OTHER THAN DIURETICS USED IN TREATMENT OF EDEMA

1. The restriction of the fluid intake and of sodium chloride.
2. The use of saline cathartics and the promotion of fluid loss through the skin with hot packs, sweat baths, etc.
3. Removal of fluid from body cavities, e.g., paracentesis for ascites.

Antidiuretics

In certain diseases like diabetes and diabetes insipidus, the amount of urine is greatly increased. Drugs that aid these diseases may properly be called antidiuretics. The site of action is more on the tissues generally than on the kidneys. It is a replacement therapy. Insulin which increases the oxidation of carbohydrates acts most probably at the site of oxidation which is the cells of the muscles and glands. Hypodermic injection of extract of the posterior lobe of the pituitary gland greatly diminishes the thirst and the volume of urine in diabetes insipidus. This effect seems to be a replacement of lessened pituitary secretion.

Action of Drugs on the Bladder

The muscular coat is strengthened at the cervix by a muscular coat which acts as the sphincter vesicae externus. When urine accumulates to a certain volume the pressure stimulates the sphincters reflexly.

The nerves governing the movements of the bladder are sympathetic and parasympathetic, consequently are affected by adrenalin and by atropine.

Adrenalin applied locally, usually causes a relaxation of the sphincters as it does the intestine, but is rarely used in medicine in any bladder condition.

In cases of enuresis when the urinary reflex is too active, belladonna derivatives are often used to lessen it. Belladonna makes effector cells connected with parasympathetic nerve endings insensitive to the normal chemical mediator and so lessens the reflex activity.

In cases of diseased or irritable bladder the emptying reflexes may be stimulated by very little filling of the organ. The patient is likely to have a frequency of urination accompanied by painful contractions. In such instances belladonna derivatives are more effective than derivatives of opium. Tincture of hyoscyamus is sometimes the preparation of choice. This drug acts like other belladonna derivatives to relax the hypertonic muscle.

Other bladder conditions may arise from lack of muscle tone. Incomplete emptying of the bladder may predispose the patient to bladder infection. Atony may be improved by pituitrin, prostigmine or one of the choline esters such as carbaminoylcholine (doryl) or acetyl- β -methylcholine chloride (mecholy). (See Chapter XII.)

Urinary Antiseptics

Urinary antiseptics are substances which when given by mouth are excreted in the urine in sufficient amounts to have an antiseptic effect on the urine and the urinary passages. The most important urinary antiseptics are methenamine or urotropin, mandelic acid, and certain sulfonamide preparations. The selection of one of these preparations in preference to another is made on the basis of careful examination of urine cultures and the type of organism found in the urine.

Methenamine, U. S. P. (Urotropin), is an artificial drug made by the action of ammonia upon formaldehyde. It occurs in the form of colorless, lustrous, odorless crystals which are freely soluble in water.

Action and Uses.—Urotropin owes its antiseptic effects to the formaldehyde which it yields in the presence of free acid. Urotropin is excreted chiefly in the urine and when the urine is acid, the drug is decomposed, liberating formaldehyde, which exerts an antiseptic action in the urine and on the surface of the mucous membrane of the genitourinary tract. When the urine is alkaline, methenamine is not decomposed and is then ineffective. Methenamine is used chiefly as a urinary antiseptic, to free the urine from microorganisms to cause the disappearance of pus. It is especially valuable

as a prophylactic against infection as a result of catheterization and in operations on the urinary organs. It is also employed to disinfect the urine of typhoid fever patients and to lessen the danger from carriers. Since the formaldehyde which it yields is very irritating to the tissues, methenamine should be used with caution in cases in which there is inflammation of the kidney or in which the acidity of the urine is abnormally high. Its value as a urinary antiseptic has perhaps been overestimated.

Administration.—The average dose of methenamine is 0.5 Gm. (7½ grains) every four hours, but double this amount may be used. The drug is administered in half a glass of water. If the urine is not acid, doses of 1 to 2 grams of sodium acid phosphate should be administered every 4 hours midway between the doses of methenamine. Enough sodium acid phosphate should be used to render the urine acid, but not enough to cause diarrhea.

Mandelic Acid (Acidum Mandelicum), N F., is closely related to benzoic acid and to salicylic acid. Recently it has had considerable use in treating infections of the genitourinary tract which are caused by intestinal organisms, *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis*, and organisms of the *Proteus*, *Pseudomonas*, *Alcaligenes*, *Salmonella*, and *Shigella* groups.* To be effective the urine must be acid, not above pH 5.5, and the concentration of mandelic acid in the urine must be 0.25 to 1 per cent. Acidity is attained by giving ammonium chloride or nitrate, sodium acid phosphate, or by a ketogenic diet. Limiting the fluid intake to 1200 cc. or less per day also aids in maintaining the concentration of the drug in the urine.

Some physicians request that citrus fruits, sodium bicarbonate, milk of magnesia, etc., be omitted from the diet of the patient since they tend to make the urine alkaline instead of acid. In therapy, the salts of mandelic acid are commonly employed. They break down in the body and liberate mandelic acid which is the bactericidal agent. It may be administered as ammonium mandelate in 10 to 20 per cent solution, in a syrup, elixir, or in a fluidextract of glycyrrhiza. Sodium and calcium mandelate are also used in medicine, the latter being dispensed in tablet form. The dose is 2 to 3 Gm. (30 to 45 grains) four times a day. Slight renal hematuria has been noted in about 2 per cent of the cases, rarely hemorrhage. Nausea, diarrhea, headache, ringing in the ears, and dysuria may

*N. N. R., 1947, p. 115.

occur. Its use is contraindicated in renal insufficiency. The only treatment usually necessary is to stop the drug and force fluids.

Sulfonamides.—Mandelic acid and methenamine have come to be supplemented as urinary antiseptics by certain members of the sulfonamide group of drugs. These preparations are usually considered to be effective against most of the gram negative organisms infecting the urinary tract and most of the gram positive cocci with the exception of *Streptococcus faecalis*.

The sulfonamides have the advantage of being easily administered and of being effective in urine of every pH found clinically. Sulfathiazole, U. S. P., and Sulfacetimide (Sulamyd-Schering) are reported to be as satisfactory as any of the sulfonamides, although a number of forms are used frequently with good results.

Although it is important that patients be watched for symptoms of poisoning (skin rash, fever, severe nausea and vomiting, etc.) they are not, as a rule, subjected to detailed and frequent blood studies as is necessary when patients are being treated for systemic infections.

If the daily dose of the sulfonamides is kept at 30-40 grains or less and the fluid intake 2000-2500 cc. daily, renal complications are said to occur rarely.*

Streptomycin, N. N. R., is reported to have limited but definite value in the treatment of infections of the urinary tract. Best results are obtained when the organism is *Proteus vulgaris* or *Aerobacter aerogenes*. Intensive treatment for a short duration appears to yield best results.† (For further discussion of this drug, see p. 435.)

Drugs Used to Increase the Acidity of the Urine

The drugs commonly used to render the urine acid when it is alkaline in reaction are sodium biphosphate and ammonium chloride.

Sodium Biphosphate, U. S. P., occurs as a white crystalline powder, having a cooling, salty and somewhat acid taste. It lowers the alkali reserve of the blood and increases the acidity of the urine. It is used especially in conjunction with urotropin, which is effective only in an acid medium. It may be given in doses of 0.6 Gm. (10 grains) well diluted in water, and repeated every two or three hours until the urine becomes acid. If it is given to assist in the action of urotropin, it should be given every four hours in larger doses (1 to 2 Gm.) midway between the administrations of urotropin.

*Pool, T. L., and Cook, E. N.: Present Concepts of Treatment of Infections of the Urinary Tract. Collected Papers of the Mayo Clinic & the Mayo Foundation 1945, p. 219.

†Nichols, D. R., and Herrell, W. E.: Streptomycin, Its Clinical Uses and Limitations, J. A. M. A. 132: 205, Sept. 28, 1946.

Ammonium chloride, like sodium phosphate, lowers the alkali reserve of the blood plasma and increases the acidity of the urine. It is given in doses of 0.3 Gm. (5 grains) every two hours. Excessive doses may cause acidosis.

Hexylresorcinol, U. S. P. See p. 273.

Drugs Used to Decrease the Acidity of the Urine

The alkaline salts, potassium acetate and potassium bicarbonate increase the alkaline reserve of the body and lessen the acidity of the urine. They are used chiefly to make the urine less acid, and consequently less irritant in cystitis. The dose is 1 Gm. (15 grains) repeated every three hours until the urine is sufficiently alkaline in reaction.

Questions for Review

1. Review the anatomy and physiology of the kidney. What is the unit of structure?
2. Mention five factors which influence the secretion of urine.
3. What is a diuretic? List the ways by which drugs may accomplish diuresis
4. Explain how each of the following acts as a diuretic:
 - a. Ammonium Chloride
 - b. Digitalis
 - c. Theobromine
 - d. Salyrgan
 - e. Theophylline
5. What is meant by a threshold substance of the urine?
6. Why is creatinine considered a nonthreshold substance?
7. Which of the diuretics mentioned in this chapter are not given by mouth?
8. Which diuretics act best in an acid environment? What preparations may be given to render the urine acid?
9. After the administration of which diuretics may the patient possibly develop symptoms of mercury poisoning? What would these symptoms be?
10. For what types of patients would you expect that the mercurial diuretics would be contraindicated?
11. Why is it advisable to dissolve methenamine in water before giving it to a patient?
12. Explain why glucose and sucrose must be given intravenously in order to obtain a diuretic effect.
13. What laboratory tests are essential to determine the therapeutic effects of the various urinary antiseptics?
14. What records are the nurses expected to keep with great accuracy when a patient is receiving salyrgan? Why?

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*Pool, T. L., and Cook, E. N.: Present Concepts of Treatment of Infections of the Urinary Tract. Collected Papers of the Mayo Clinic & the Mayo Foundation. 1945, p. 219.

†Nichols, D. R., and Herrell, W. E.: Streptomycin, Its Clinical Uses and Limitations. J. A. M. A. 132: 205, Sept. 28, 1946.

play a relatively feeble role. All adrenergic drugs, however, dilate the pupil (strong light may prevent this by contraction of the circular muscles). Cocaine will also cause dilation, partly by stimulation of the sympathetics, partly by paralysis of the parasympathetics. Fear, excitement and most strong emotions cause dilation by increasing cortical inhibition of the oculomotor center.

The circular muscle of the iris is under control of the parasympathetics. The fibers of this system leave the brain in the third nerve, pass to the ciliary ganglion, and thence to the circular (lenticular) muscle of the iris. All cholinergic drugs act on the parasympathetics to the eye. Cholin, muscarine, pilocarpine, and eserine stimulate it, and cause a small pupil. The atropine group paralyzes it and causes a dilation of the pupil.

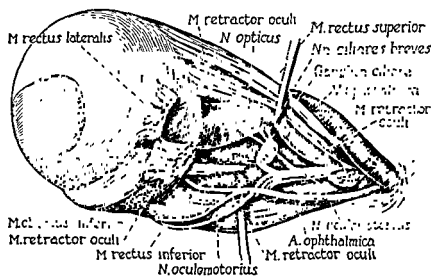


Fig. 30.—Dissection to show the ciliary ganglion and other orbital structures behind the eyeball. (From Cooper and Groot: *J. Lab. & Clin. Med.* 6: 630, 1921.)

Color Blindness.—Congenital disturbance of color sense has been found in about 3 per cent of examinations made for this purpose. It is extremely rare in females (0.2 per cent). Total color blindness is extremely rare. Most cases are concerned with one of the three fundamental colors: blue, green, and red.

Amblyopia is a term used to signify dimness of vision, and amaurosis means loss of vision. These conditions may be congenital or they may be produced by drugs, disease, or trauma. Drugs that may cause damage to vision are quinine, ethyl hydrocupreine (optochin), male fern, methyl alcohol, arsenical preparations, nicotine, alcohol, lead, carbon bisulfide, iodoform, nitrophenol, dinitrophenol,

UNIT IX

CHAPTER XVIII

PHARMACOLOGY AS RELATED TO THE EYE

The eye may be said to be comprised of essential and accessory organs or structures. The essential organs are the eyeball, the retina, and optic nerve. The accessory organs are designed to protect the essential organs and aid in their function. They are the eyelids, conjunctiva, lacrimal glands, and ocular muscles.

The retina or nervous tunic is the light-sensitive coat of the eye. Embryologically it is a part of the brain, and the optic nerve is a cerebral tract. The retinal ganglionic layer in its relation to the brain is similar to the spinal sensory ganglion cells. The peripheral parts are receptive endings, and the optic nerve is a continuation centralward of the afferent nerve.

The retina is composed essentially of three kinds of cells: (a) the rod and cone visual or light-sensitive elements, (b) a middle stratum of bipolar cells, and (c) an interior layer of ganglion cells. The distribution of these is not uniform throughout the retina. At the entrance of the optic disk the rods and cones are absent, and light projected on this area gives no visual sensation. This is the blind spot of the retina. The rods and cones connect with the bipolar neurons, and these in turn with retinal ganglion cells which form the optic nerves. This explains why drugs like arsenic, methyl alcohol, male fern, quinine, nicotine, santonin, naphthols, etc., that injure the retina, may also injure the optic nerve.

Internal Muscles of the Eye.—Two sets of muscles govern the size of the pupil. These are circular and radiating, which make up the iris. The ciliary body (from *cyclos*, a circle) is a ring of tissue joined to the choroid behind and to the iris in front. The iris is a muscular diaphragm arising from the ciliary body.

The iris has a double nervous control, typical of all unstriated muscle and glands, i.e., sympathetic and parasympathetic. The sympathetic control passes from the upper dorsal nerves to the sympathetic cord, and to the inferior cervical ganglion, thence to the middle and superior cervical ganglion, and to the radiating fibers in the iris. These radiating fibers are very thin and weak, hence

pupil. Asphyxia may paralyze the centers and in this way cause a sudden dilation of the pupils. Morphine, by depressing impulses acting on this center, allows it full freedom of action and a small pin-point pupil results. Atropine, because it acts peripherally, removes the miosis, while cocaine, which acts on the sympathetics, has hardly any effect.

SUMMARY OF NERVE SUPPLY OF THE EYE

	PARASYMPATHETIC	SYMPATHETIC
Center in brain	In corpora quadrigemina	Hypothalamus and I and II dorsal
Nerves—medullated	Third nerve	I, II, and III dorsal
Ganglia	Ciliary	Cervical Sympathetic
Action on eye	Constricts pupil by action on ciliary muscle	Dilates pupil by action on striated muscle. Produces exophthalmos. Constricts vessels of eye

The Lacrimal Glands

The lacrimal glands are supplied by both sympathetic and parasympathetic nerves. There are centers for lacrimal secretion in the medulla from which sympathetic fibers pass down to the first, second, and third thoracic nerves, and by way of the superior cervical ganglion to the lacrimal glands. Parasympathetics from the facial nerve pass via the sphenopalatine gland to reach the lacrimal gland. The lacrimal gland is a serous gland and secretes a watery fluid slightly alkaline or neutral in reaction. Besides sodium chloride and traces of other salts, it contains a ferment which inhibits bacterial growth.

Function of Tears.—Tears lubricate the cornea, keep it clean, remove small foreign particles, and help to maintain the transparency of the cornea.

Drugs Used in the Eye

Locally acting drugs in the eye act as in other places but because of the sensitivity and great vascularity, their action may be greater.

Antiseptics.—Antiseptics used in the eye must be mild.

Collyria (eyewashes).—

1. Saturated boric acid solution
2. Argylol 10 to 20 per cent
3. Silver nitrate $\frac{1}{2}$ to 1 per cent
4. Aqueous metaphen 1:2500
5. Zinc sulfate $\frac{1}{10}$ to 1 per cent

etc. The pathologic changes are entirely peripheral and concerned not with the retinal coloring matter. Central changes do not seem to cause colored vision.

Night Blindness, Nyctalopia.—Night blindness may be due to a variety of causes, such as exposure to strong light or glare, but the important pharmacologic or physiologic cause seems to be poor nutrition, especially a lack of vitamin A, and is associated with a scorbutic state. Cod-liver oil is indicated in the treatment.

Hemeralopia, or day blindness, is a symptom characterized by the fact that the subject sees better on dull, dark days than in bright light. The usual field is not contracted. It may have the same cause as nyctalopia, but occurs also in affections of the optic nerve and in some diseases of the retina. It may be present in certain congenital anomalies, such as albinism, coloboma of the iris and choroid, and in irideremia (absence of the iris). Liver as a treatment of hemeralopia is mentioned by Pliny (Meyer and Gottlieb).

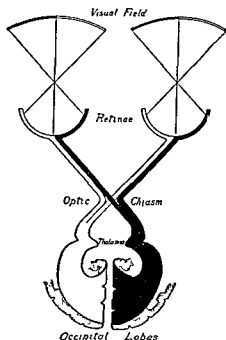


FIG. 31.—Afferent paths connecting the retinae with the visual area of the cerebral cortex. (From Bard: *Macleod's Physiology in Modern Medicine*.)

Oculomotor Center.—The efferent fibers of the third nerve originate in the Edinger-Westphal nucleus in the midbrain. The efferent fibers terminate as preganglionic fibers in the ciliary ganglion, from which postganglionic fibers pass to the constrictor muscles of the

radial fibers, while the stronger circular constrictors are still functioning. Adrenalin acts in the same manner and the evidence in favor of their action on the sympathetics is similar, except that cocaine which is a local anesthetic may act in stronger solutions on all nerves to cause some paralysis. Cocaine is not used in practice to dilate the pupil, since atropine acts more strongly and is more effective.

Cocaine is a good anesthetic for a cataract operation and for the removal of foreign bodies from the cornea.

Myotics.—Myotics are drugs which lessen the size of the pupil due to contraction of the ciliary muscles of the eye. The drugs commonly used for this purpose are physostigmine salicylate and pilocarpine hydrochloride. The action is on the endings of the third nerve to the muscle.

Main differences between pilocarpine and physostigmine on the eye: Physostigmine is a stronger miotic than pilocarpine because it acts on both nerve endings and muscle. Physostigmine is stronger in removing the effects of atropine. Pilocarpine directly stimulates the nerve endings, while physostigmine acts more as a sensitizer, so that the normal impulses passing over the nerve exert a greater action on the muscle.

Administration.—The average dose of physostigmine is 0.002 Gm. ($\frac{1}{30}$ grain). To restore the pupil to normal after the use of a mydriatic, one drop of a 0.1 per cent solution is used. To treat glaucoma and other eye diseases, solutions varying in strength from 0.1 to 1.0 per cent are employed, usually with the admixture of cocaine.

Pilocarpine is used in solutions of 0.5 to 1 per cent as a weak myotic in diseases of the eye such as glaucoma and corneal ulcer.

Uses for Myotics.—The action of the myotics is exactly opposite or antagonistic to that of the mydriatics. They stimulate the effector cells of the circular and ciliary muscles of the eye, thus causing contraction of the pupil and accommodation for short distances. Because of this antagonistic action, they are used to restore the eye to normal after the use of atropine, homatropine, etc. They are employed chiefly in the treatment of eye diseases to contract the pupil and to reduce intraocular tension and soften the eyeball. For the latter purpose, it is valuable in glaucoma, a disease which is characterized by hardening of the eyeball. The myotics are also used in the treatment of peripheral ulcer of the cornea.

Ointments.—

1. Boric acid ointment
2. Yellow oxide of mercury $\frac{1}{2}$ to 1 per cent
3. Bichloride of mercury ointment $\frac{1}{50}$ per cent
4. Metaphen ointment 1:3000

Anesthetics.—

1. Cocaine 2 to 4 per cent
2. Procaine and apothesine $\frac{1}{2}$ to 2 per cent
3. Butyn $\frac{1}{2}$ to 2 per cent

Mydriatics.—Mydriatics are drugs which dilate the pupil and relax the accommodation of the eye. Many drugs given systemically for other purposes produce dilatation of the pupil, but there are a few which may be given locally for this purpose alone. The most important mydriatics and their doses are the following:

Atropine sulfate	0.5 mg. ($\frac{1}{120}$ gr.) $\frac{1}{4}$ -2%
Homatropine hydrobromide	0.5 mg. ($\frac{1}{120}$ gr.) $\frac{1}{2}$ -1%
Scopolamine hydrobromide	0.5 mg. ($\frac{1}{120}$ gr.) $\frac{1}{4}$ -1%
Cocaine hydrochloride	0.015 Gm. ($\frac{1}{4}$ gr.)

The mydriatics dilate the pupil by paralyzing the effector cells of the circular muscle which contracts the pupil and thus increases the activity of the radial muscle which has the opposite function. They also paralyze the effector cells of the ciliary muscle which controls accommodation, or the power of the eye to change its focus for near and distant objects. The patient is then unable to see objects near at hand.

The mydriatics are used by ophthalmologists to facilitate the examination of the eye with the ophthalmoscope, and to prevent the spread of inflammation of the iris, or the formation of adhesions between the iris and the lens. They may be given internally or dropped into the conjunctival sac. When they are given internally, the mydriatic effect is due to the drug carried by the blood, and is bilateral. When the drug is applied locally, the effect is unilateral. The drugs produce their effects in from one to two hours. These effects may last several days after the administration of atropine sulfate, which is consequently less desirable for diagnostic purposes but of more value in preventing the spread of inflammation or the formation of adhesions. Homatropine and hyoscine produce similar but less lasting effects and are more suitable for eye examinations.

Cocaine.—The dilation of the pupil is much less than with atropine. This is because cocaine stimulates the nerves to the much weaker

UNIT X

CHAPTER XIX

PHARMACOLOGY AS RELATED TO THE REPRODUCTIVE SYSTEM

The great urge of nature is that every living object seems driven to convert all matter into its own specific living matter. This involves reproduction. In reproduction the uterus is the most important organ in the mammal. Its response to drugs varies widely in different species, which increases the difficulty in ascertaining the action of drugs on the human uterus.

Movement of the Uterus

The activity of uterine muscle shows cyclical changes. These are different in diestrus and estrus. Profound changes occur during pregnancy. The human uterus increases in weight during the first pregnancy from about 50 grams to 1000 grams. Its capacity increases from about 5 cc. to 5000 cc. The individual muscle fibers increase about tenfold in length and new fibers may be formed. These changes are accompanied by many changes in the response to drugs. For this reason in standardizing drugs that act on the uterus, the virgin uterus of the guinea pig or rabbit is used.

The uterus both in situ and when excised contracts rhythmically. Both pendulum and peristaltic movements may be seen. In non-gravid animals the peristaltic movements are relatively slight, with alternate pauses, such as are seen in the intestine. These vary greatly with the condition of sexual activity. They are depressed by early pregnancy, but increase in later pregnancy. Parturition is accomplished by powerful peristaltic waves which cause the labor pains. The uterine movements are myogenic in origin, and are not abolished by section of the uterine nerves. The activity, however, is controlled by extrinsic nerves.

Innervation

The innervation of the uterus is essentially sympathetic through the hypogastric nerve. The innervation is peculiar in that both excitor and inhibitor nerves are sympathetic. These nerves come

Glaucoma.—In glaucoma the most marked symptom is an increase in intraocular pressure. The pressure in the normal eye does not exceed 26 mm. of mercury. A higher pressure causes pain, pathologic changes, and disturbance of vision. It is believed that the intraocular fluid is a secretive dialysate from the capillaries or the ciliary body, and that there is a continuous circulation which passes into the anterior chamber and is drained away by veins in the canal of Schlemm in the angle between the iris and the cornea. In glaucoma the circulation is deranged and the fluid accumulates in the eyeball. Physostigmine, by an action on the ciliary muscle, which apparently opens the circulatory paths, decreases the intraocular pressure. In the treatment of glaucoma, two to three drops of a 0.5 per cent solution are instilled into the conjunctival sac two or three times a day. Pilocarpine is used for the same purpose, but it is less active. Atropine increases the intraocular pressure, hence it is important not to give atropine in cases of high intraocular pressure.

Colored Vision

Xanthopsia, or yellow vision, occurs in jaundice. It is a rather common symptom of santonin poisoning, less so in poisoning from digitalis and amyl nitrite, picric and chromic acids.

Colored vision cannot be explained satisfactorily because the central mechanisms by which color sensations are created are not definitely established, as is evident from the numerous theories of color vision still held.

kill the mother than to produce abortion. Most of the drugs used are organic irritants, like oil of savin, tansy, or pennyroyal, and anthracene purgatives. Their effect is due reflexly to the gastro-enteritis they produce. Ergot has been used, but if it has any effect, it requires long-continued and dangerous doses. Quinine is credited by some with the power of producing abortion, but moderate doses may be given to pregnant women in malarial districts, since an attack of malaria is as likely to produce that effect. Lead salts are frequently used to produce abortion and chronic lead poisoning is known to cause abortion. Lead is muscle poison. It causes contraction of most plain muscle in the body but particularly of the colon. These colicky contractions of the colon may be somewhat relieved with atropine.

Oxytocics, or Ecboolics.—These are drugs that hasten parturition by strengthening uterine contractions. Many substances exert such an action, the mode of which in many cases is not known. Drastic cathartics and some volatile oils stimulate the uterus reflexly through irritation of the intestine.

The ecboolics most used are ergot, pituitrin, and quinine. These produce their effect mainly by direct stimulation of the uterine muscle. Part of the selective action is to be explained on the heightened sensitization of the organ during pregnancy.

Ergot

Ergot is the dried sclerotium (mycelium) of the parasitic fungus *Claviceps purpurea*, which grows on many species of grain, but especially on rye, where it forms the long black bodies which, after a wet summer, are often seen in the ears of the rye.

Active Principles.—The composition of ergot is very complex. In addition to a number of potent alkaloids, ergot contains several amines, acetylcholine, and some choline derivatives. At least ten alkaloids have been identified, the more important of which are *ergotamine*, *ergonovine* (ergometrine), and *ergotoxine*. The pharmacologic actions of ergotamine and ergotoxine are very similar but both differ from ergonovine in a number of respects.

Pharmacologic Action.—The most important sites of action of the alkaloids of ergot are on the smooth muscles of the uterus and the blood vessels.

1. ERGOTAMINE AND ERGOTOXINE.—

a. *On the Uterus.*—Ergotoxine and ergotamine exert their most powerful effect on the uterus. The mechanism of action is a direct

from the second, third, and fourth lumbar nerves, and pass through inferior mesenteric ganglion and through the hypogastric nerve to the uterus. The parasympathetic fibers arise from the first, second, third, and fourth sacral roots, unite in the hypogastric plexus, from which fibers go to the uterus, bladder and rectum. These two systems, the sympathetic and the parasympathetic, unite in the uterus to form the Frankenhauser plexus utero vesicalis. In animals in which sympathetic stimulation causes contraction, parasympathetic stimulants, such as physostigmine and acetylcholine, usually increase the uterine movements, and atropine depresses. This is somewhat similar to the action of pilocarpine and atropine in the sweat glands. When the sympathetic response is inhibitory the action of parasympathetic stimulants is inconstant, though atropine usually depresses

Reflex Increase of Uterine Movements

A number of drugs, especially in excessive and dangerous doses, may produce reflex stimulation of the uterus. Such drugs are drastic cathartics and irritant volatile oils. Any action these produce would seem to be due to reflexes, and to pathological changes in the circulation of the pelvic organs. Many drugs, such as peptones and organ extracts, if given intravenously cause similar harmful circulatory changes.

Hormonic Control of the Female Reproductive Organs

Recent work has shown the interdependence of the female sex organs and the complex system of endocrine glands. The most outstanding of these relationships is discussed under Hormones.

Uterine Sedatives

In labor, contractions are delayed by all narcotics and hypnotics, even when the concentration is insufficient to act directly on the uterus. Threatened abortion may be treated by central nerve sedatives, but few drugs are known that will long delay uterine contractions. The contractions are delayed somewhat by all drugs that relax smooth muscle, such as atropine, papaverine, and the nitrites. It is probable that some of the sex hormones will prove useful in this field, especially in threatened abortion.

Abortifacients

Abortion is a common mishap of pregnancy and occurs in about one in five cases. A number of drugs have been used to produce criminal abortion, all of which are dangerous and more likely to

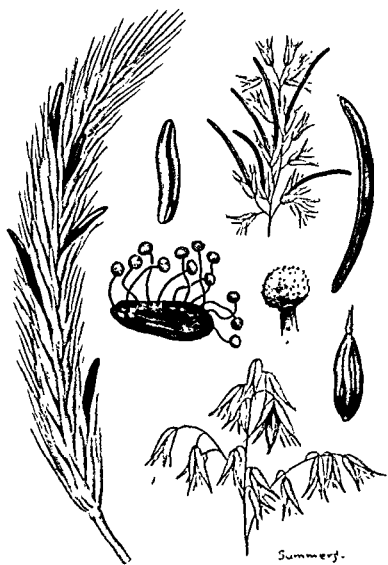


PLATE XIV.—*Claviceps purpurea* (Rye ergot). (From Jackson *Experimental Pharmacology and Materia Medica*.)

muscular stimulation since it occurs in the uterus after removal as well as when it is in the body.¹ Small doses produce normal uterine contractions followed by relaxation but large doses produce powerful contractions which may be spastic in nature. A gravid uterus is more sensitive to the alkaloids of ergot than a nongravid or immature uterus. Ordinary therapeutic doses of the alkaloids produce an effect in the gravid or parturient uterus that is unaccompanied by side actions.

b. *In the Circulatory System.*—The action on blood vessels is a direct muscular constriction particularly of the smaller vessels. This effect is of value in reducing uterine hemorrhage after childbirth. When ergotamine and ergotoxine are administered in large doses, there follows a definite rise in blood pressure. The effect on blood pressure is less powerful than that of epinephrine but it lasts longer.

Both ergotamine and ergotoxine are capable of damaging the capillary epithelium which in turn may give rise to thrombosis and possibly gangrene. Man is particularly sensitive to this toxic effect of the alkaloids of ergot.

c. *Sympathetic Nervous System.*—Ergotamine and ergotoxine act as autonomic blocking agents to paralyze the effector cells and make them nonresponsive to sympathin or adrenalin. This action is not significant in man, provided the dosage remains in therapeutic limits

2. **ERGONOVINE (ERGOMETRINE).**—Ergonovine resembles ergotamine and ergotoxine in its effect upon the uterus although it appears to have a greater selective action on uterine muscle and produces its effects more rapidly. Ergotamine and ergotoxine are poorly and irregularly absorbed from the gastrointestinal tract while oral doses of ergonovine are readily absorbed, and it is therefore effective in smaller doses and weaker concentrations than the other alkaloids. Because small doses are effective and because the parturient uterus is especially sensitive to ergonovine, side actions rarely accompany its use in obstetrics. Its duration of action is thought to be somewhat less than that of the other two alkaloids.

Ergonovine differs from ergotoxine and ergotamine in that it appears to stimulate the effector cells connected with adrenergic nerves rather than paralyze them. It produces little or no rise in blood pressure and while it shares with the other alkaloids the ability to cause gangrene, it appears to be definitely less toxic than ergotamine and ergotoxine.

¹Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co. p. 657.

Therapeutic Uses.—Ergot is administered orally in the form of fluid extract but preparations of the alkaloids are also available. Fluidextract has the disadvantage of being unstable and liable to deterioration. It is now known that its desirable properties are due mainly to the presence of ergonovine.

Preparations of ergot are used primarily to promote involution of the uterus and to prevent or control postpartum hemorrhage. Oxytocics should not be used during the first and second stages of labor. The contractions which these drugs produce are such that the life of the mother and the fetus may be endangered by their use.

Ergotamine tartrate has also been advocated for the relief of certain types of headache and to relieve excess itching associated with jaundiced conditions.

Preparations.—

Fluidextract of Ergot (Fluidextractum Ergotae), N. F. Dosage: 2 cc. (30 minims) orally.

Ergotamine Tartrate (Ergotaminae Tartras), U. S. P. (Gynergen—Sandoz). Dosage: Intramuscular, 0.5 mg. ($\frac{1}{20}$ grain); oral, 1 mg. ($\frac{1}{60}$ gr.).

Ergonovine Maleate (Ergonovinae Maleas), U. S. P. (Ergotrate—Lilly). Dosage: 0.5 mg. ($\frac{1}{120}$ grain) orally; 0.2 mg. ($\frac{1}{300}$ gr.) intravenously or intramuscularly.

Ergot Aseptic, N. N. R. Standardized biologically to have the same potency as Fluidextract of Ergot. Dosage: 1-2 cc. (15-30 minims) intramuscularly.

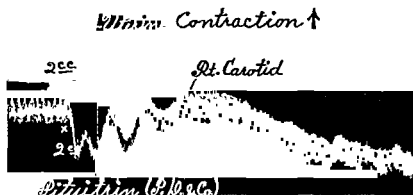
Ergot Poisoning.—Acute ergotism is very rare, and generally follows attempts at abortion. The toxic symptoms are rapid pulse, itching, tingling, thirst, vomiting, diarrhea, headache, confusion, or unconsciousness. Hemorrhage from uterus and abortion are of frequent occurrence. Gangrene is exceptional, but after a single dose it has supervened in small areas, such as the toes.

Chronic ergotism, *ergotismus chronicus*, is now of rare occurrence where modern milling methods are used, but before the cause was known, it was frequent in wet seasons and poor harvests, especially in Russia, due to ergot in the grain.

Chronic ergotism may occur in two forms: gangrenous and convulsive. The gangrene depends on the prolonged constriction of the vessels, and at the same time the vessels fill with a hyaline substance that blocks the circulation. Prolonged constriction of cerebral blood vessels results in degenerative changes in the brain. Constriction in retinal vessels may cause blindness.

The most striking symptom of ergotism is the dry, painless gangrene of some part of the body such as fingers or toes. The part affected first becomes cold, numb and dark in color, and then shrivels up and drops off without pain or bleeding. These symptoms are due to the fact that the blood supply to the





Dilution = 1-5.

Dog:—18 Kilos:—Closed Ether Anesthesia

Uterus in situ.



Fig. 32.—Tracing showing the action of pituitrin on the uterine contractions and blood pressure in a dog. Ergot elicits a similar effect. (From Jackson: *Experimental Pharmacology and Materia Medica*.)

2. HEART AND BLOOD VESSELS.—Extracts of the posterior pituitary, especially preparations rich in the pressor principle, have been known to bring about a marked rise in blood pressure. The action is a direct one on the small arteries and capillaries. The rise in pressure is not as great as that seen after epinephrine but it comes

part is shut off by the constriction of the vessels. The disease was called "St. Anthony's fire," "holy fire," or "hell fire." The cure at that time was a pilgrimage to the shrine of St. Anthony, hence the name.

Convulsive Ergotism.—The first symptoms of convulsive ergotism are: depression, weakness, drowsiness, headache, giddiness, painful cramps in the limbs, itching, and formication. In some cases paroxysmal convulsions set in, which are generally clonic but sometimes epileptiform. Some intellectual weakness follows recovery from this form of ergot poisoning.

Treatment.—Treatment amounts to the immediate withdrawal of the ergot preparation and symptomatic measures. Improved circulation to the parts affected is the main aim of treatment. Vaso-dilators, such as the nitrites and papaverine, are therefore resorted to. In case of gangrene, the usual medical or surgical measures are employed.

Posterior Pituitary

Extracts of posterior pituitary are obtained from the corresponding glands of cattle and sheep. The pituitary body is a small ductless gland situated in a cup-shaped depression in the sphenoid bone at the base of the brain, and consists of two lobes, the anterior and the posterior. The commercially prepared extract of the posterior lobe is known as pituitrin. Pituitrin is known to contain active principles which when given parenterally have the following effects in the body, (1) stimulation of uterine muscle (oxytocic effect), (2) promotion of water absorption in the tubules of the kidney (anti-diuretic effect), and (3) constriction of peripheral blood vessels (pressor effect).

A preparation rich in oxytocic principle is marketed as "pitocin" and one containing a predominance of pressor and anti-diuretic principle is known as "pitressin." The above-mentioned principles are thought to be pituitary hormones although their hormone status has not been conclusively established in each case.

Pharmacologic Action.—

1. ON THE UTERUS.—The oxytocic principle as present in pitocin directly stimulates the uterine muscle and produces rhythmic contractions. Its action in the human being is modified by the pregnant or nonpregnant state of the uterus as well as by the stage of pregnancy. Sensitivity to the extract increases as pregnancy progresses. The muscle of the fundus of the uterus appears to be more sensitive than that of the cervix. The effects of the preparation come on rapidly after administration as contrasted with ergot which acts more slowly. Pituitary extracts and ergot are sometimes combined to secure both the rapid and the more gradual effects.

2. Solutions containing the pressor principle are used to relieve intestinal ileus, distention and gas pain following surgical operations, and infectious diseases.

3. Pituitary extracts containing the antidiuretic principle are useful to relieve the thirst and polyuria associated with diabetes insipidus. The preparation may be administered hypodermically, intramuscularly, or intranasally. In the latter case, solution of the extract is placed on small cotton pledgets and applied against the nasal mucous membrane or small amounts of a powder form are snuffed up on to the membrane.

4. Pituitary extracts have been used in the treatment of shock but their value is questionable. They are contraindicated in patients having vascular disease.

Preparations.—

Posterior Pituitary Injection, U. S. P. Dosage: 1 cc. (15 minims) intramuscularly. This preparation is the one ordinarily employed in obstetrics and is known as obstetrical pituitrin. It contains all of the active principles. When given to surgical patients 1-2 cc. are given subcutaneously or intramuscularly.

Ampoules of Pitocin, N. N. R. Dosage: 0.3-1 cc. (5-15 minims) intramuscularly. An aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland. Its use is particularly indicated when increase in blood pressure is not desired.

Ampoules of Pitressin, N. N. R. Dosage: 0.3-1 cc. (5-15 minims) intramuscularly. An aqueous solution containing the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland. The pressor activity is twice that of the U. S. P. posterior pituitary injection.

Emmenagogues

Emmenagogues are drugs which induce or increase menstruation. Many of the irritant cathartics, such as aloë and aloin, and the drastic cathartics may produce this effect. The blood tonics, iron, arsenic, liver extract, etc., which improve the general physical condition may also increase menstruation. A group of drugs obtained from pennyroyal, cotton root bark and other common herbs are used as household remedies for this condition. Their action is due to volatile oils which they contain. Such drugs have been used largely on an empiric basis and have never had a secure status in good therapeutics.

on more slowly and lasts longer. The heartbeat is frequently slower and stronger, although its response is variable. It may be depressed either because of direct action on the myocardium or by impaired nutrition due to constriction of the coronary arteries.

The rise in blood pressure is frequently rather slight and occasionally an actual lowering of blood pressure occurs. It is thought that the cardiovascular reflexes are able to overcome the peripheral effects of the drug on the circulatory system.

3. **INTESTINE.**—Although the action of posterior pituitary extracts on the intestinal musculature is variable and investigators are not entirely in agreement, recent workers report that both the oxytocic and pressor principles stimulate the muscle of the entire intestine. Motility is increased without much change in the tone. The onset is rapid and lasts approximately one hour.

4. **MAMMARY GLANDS.**—Posterior pituitary extract is known as a galactagogue because it temporarily accelerates the output of milk obtainable from lactating mammals. It does not affect the total amount of milk formed over a prolonged interval of time. The action is apparently a direct one upon the smooth muscle of the gland ducts, causing them to empty more completely.

5. **URINARY ORGANS.**—Pituitary extract which contains the pressor principle decreases the secretion of urine. This action seems to be accomplished by stimulation of the reabsorptive activity of the tubule cells of the kidney. This effect is produced in the patient suffering from diabetes insipidus but not in a person with a normally functioning kidney. The bladder musculature is stimulated, especially if it has previously been in an atonic condition.

Administration.—Oral administration of pituitary extracts are ineffective, but they are readily absorbed after parenteral injection.

Therapeutic Uses.—

1. **In Obstetrics**—Posterior Pituitary Injection and Pitocin are used to increase contractions of the uterus at the time of childbirth. They may be used in a long labor when normal contractions do not bring about expulsion of the fetus or to constrict the uterus and decrease hemorrhage after delivery of the placenta. Their use should be attended with caution and their use avoided when the cervix is not thoroughly effaced and easily dilatable. Their use is contraindicated during the first stage of labor. If used when the cervix is undilated and rigid, severe laceration and excessive trauma are very likely to result. Ill-advised use of oxytocics is thought to explain high maternal and infant mortality rates in this country.

2. Solutions containing the pressor principle are used to relieve intestinal ileus, distention and gas pain following surgical operations, and infectious diseases.

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Recently various endocrine preparations have been prescribed for a number of menstrual disorders. It is important that organic disease be ruled out before such therapy is instituted. Endocrine therapy has been very satisfactorily used for some patients while others have apparently received little benefit.

Sex Hormones

The activities of the body tissues are regulated by the endocrine system as well as by the nervous system. The latter enables the body to make rapid adjustments in both the internal and external environment while the former brings about a slower adaptation to environmental conditions.

The endocrine glands are physiologically well integrated and exert widespread effects of such extent that no organ or even part of an organ escapes their influence. All hormones are probably necessary for the normal development and function of the reproductive system. Some endocrine secretions stimulate activity while others inhibit or correlate a number of reactions. The following classification taken from Davison¹ includes the sex hormones which have an effect on the reproductive system as well as those which are made by the gonads.

A. Anterior Pituitary

1. Pituitary Gonadotropic Hormones
 - a) Follicle-stimulating Hormone (Prolan A)
 - b) Luteinizing Hormone (Prolan B)
2. Lactogenic Hormone (Prolactin)

B. Gonadotropic Hormones From Sources Other Than the Pituitary

1. Chorionic Gonadotropic Hormone
2. Equine Gonadotropic Hormone

C. Ovarian Hormones

1. Estrone (Theelin)
 2. Estriol (Theelol)
 3. Estradiol
 4. Diethylstilbestrol (stilbestrol)
 5. Hexestrol
 6. Octofollin
- } new synthetic estrogens
7. Progestational Compounds (Corpus Luteum Hormone)
 - a. Progesterin (natural)
 - b. Progesterone (synthetic)
 - c. Pregneninolone

D. Male Sex Hormones

1. Androsterone (natural)
2. Testosterone (synthetic)

¹Davison, F. R.: *Synopsis of Materia Medica Toxicology and Pharmacology* St. Louis, 1944, The C. V. Mosby Co., p. 630.

Pituitary Gonadotropic Hormone

The endocrine gland which exerts the chief gonadotropic influence in the body is the anterior lobe of the pituitary. How many hormones are made by this part of the gland is not definitely known, but most observers acknowledge the existence of a follicle-stimulating hormone and a luteinizing hormone. If these substances are deficient or absent the reproductive organs, as well as the accessory organs, fail to develop and function normally. Their origin is believed to be from the basophilic cells in the anterior portion of the pituitary gland.

The follicle-stimulating hormone is responsible for the liberation of estrin and the luteinizing hormone brings about the formation of progesterin in the female. In the male, the follicle-stimulating hormone promotes the development of sperm cells and the growth of the seminiferous tubules. The luteinizing hormone in the male stimulates the formation of testosterone, a male sex hormone.

The clinical use of the pituitary gonadotropic hormones has been handicapped by the lack of sufficiently refined preparations. Commercial preparations often contain proteins and other inert substances which make injections painful and the patient prone to develop allergic reactions.

Some degree of success has accompanied the use of these gonadotropic extracts when used in the treatment of amenorrhea, Fröhlich's syndrome, sterility, undescended testicle (cryptorchidism), and hypogenitalism. Lack of success in treatment can sometimes be attributed to the fact that when a deficiency of one of the pituitary hormones exists it is more than likely that there is a deficiency in a number of others which may not be of a direct gonadotropic nature.

Preparations.—

There are no official gonadotropic preparations from the anterior pituitary gland.

Gonadophysin (Scarle) is an anterior pituitary preparation from sheep glands containing both gonadotropic factors. Dosage: 0.5-1.5 cc. daily or every other day given intramuscularly.

Prephysin (Chappel) contains the follicle-stimulating hormone and a small amount of the luteinizing factor. Dosage: 0.5-1 cc. (8-15 minims).

Anterior Pituitary Gonadotropic Factor (Armour) contains the gonadotropic factors and also a small amount of other anterior pituitary factors. Dosage: 1-2 cc. intramuscularly every one or two days until 20 cc. are given.

The Lactogenic Hormone

Although the lactogenic hormone has been isolated from the other anterior pituitary constituents, it is little used clinically. There are simpler ways of nourishing the human infant than to regulate the pituitary function and hence the milk production of the human mother. The lactogenic hormone is capable of initiating and promoting milk secretion in the mammary gland which has previously been primed by the effects of the ovarian hormones. It is available as "Prolactin" (Schering).

Gonadotropic Hormones From Sources Other Than the Pituitary

1. Chorionic Gonadotropic Hormone.—A gonadotropic substance which forms the basis of pregnancy tests (Friedman and Aschheim-Zondek tests) is found freely in the urine of gravid females. This substance was originally thought to come from the anterior pituitary gland. It is now conceded that the placenta is the source. The action of the chorionic gonadotropic substance is different from that of the anterior pituitary gland.

There is no evidence to show that these substances alone are capable of stimulating ovarian function in primates.¹ This fact is significant because preparations of gonadotropic hormones often contain the chorionic factor and are marketed with little or no distinction between the two types (chorionic and pituitary).

The reason that pregnancy urine can be used to test for the gravid state is that the laboratory animal that is used is usually a rodent and in these animals the chorionic gonadotropic factor does stimulate follicular growth as well as development of the corpus luteum.

Reliable investigators have observed degenerative changes in the ovaries of women and monkeys who have received injections of chorionic gonadotropin.* It also exerts an effect on the interstitial cells of the testicle in the male, causing the formation of more male hormone (androgen) which in turn stimulates the growth of accessory sex organs.

Chorionic gonadotropin has been used for a variety of conditions, many times inadvisedly.

Uses.—

1. In the treatment of cryptorchidism (undescended testicle) when there is no anatomic obstruction to prevent testicular descent.

¹Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*. 1941, p. 1186.

*N. N. R., 1947, p. 374.

2. It is being used experimentally in the treatment of hypogonadism and functional uterine bleeding, but there is considerable difference of opinion about its value.

Preparation.—

Chorionic Gonadotropin, N. N. R. (Follutein). A water-soluble gonadotropic substance obtained from the urine of pregnant women. It is a glycoprotein containing about 12 per cent galactose. The dosage used in treating cryptorchidism is 200-500 international units two or three times a week. Therapy should be discontinued if there are signs of precocious maturity.*

2. **Equine Gonadotropic Hormone.**—The blood serum of pregnant mares is a rich source of gonadotropic hormone which is presumably of chorionic origin but unlike human chorionic gonadotropin, it does not gain access to the urine in appreciable quantity. Its gonadotropic activity resembles that of the anterior pituitary. It exerts a stimulating effect on ovarian growth and activity, particularly that of ovulation. It likewise stimulates activity of the testes.

It is possible to obtain preparations which are so refined that very little protein substance accompanies the active constituents. Its use has been recommended for a number of conditions including menstrual disorders, cryptorchidism, sterility, and sexual development.

Preparations.—Preparations of pregnant mare serum are not official and are marketed under the names of Gonadogen (Upjohn) and Gonadin (Cutter). These preparations are usually administered intramuscularly.

Ovarian Hormones

The ovaries are the female sex glands which are situated on either side of the uterus. They not only develop and periodically discharge the ripened ova but also secrete the ovarian hormones.

One of the ovarian hormones is made by the cells of the graafian follicle and is referred to as the follicular hormone. The other is the luteal hormone made by the cells of the corpus luteum. Normal development and activity of the reproductive organs are dependent in part on the right state of balance between these hormones. They are secreted in sequence under the influence of the gonadotropins of the anterior pituitary gland.

FOLLICULAR HORMONE

The follicular hormone is responsible for the development of the sex organs at puberty and for the secondary sex characteristics such

*N. N. R., 1947, p. 375.

The Lactogenic Hormone

Although the lactogenic hormone has been isolated from the other anterior pituitary constituents, it is little used clinically. There are simpler ways of nourishing the human infant than to regulate the pituitary function and hence the milk production of the human mother. The lactogenic hormone is capable of initiating and promoting milk secretion in the mammary gland which has previously been primed by the effects of the ovarian hormones. It is available as "Prolactin" (Schering).

Gonadotropic Hormones From Sources Other Than the Pituitary

1. **Chorionic Gonadotropic Hormone.**—A gonadotropic substance which forms the basis of pregnancy tests (Friedman and Aschheim-Zondek tests) is found freely in the urine of gravid females. This substance was originally thought to come from the anterior pituitary gland. It is now conceded that the placenta is the source. The action of the chorionic gonadotropic substance is different from that of the anterior pituitary gland.

There is no evidence to show that these substances alone are capable of stimulating ovarian function in primates.¹ This fact is significant because preparations of gonadotropic hormones often contain the chorionic factor and are marketed with little or no distinction between the two types (chorionic and pituitary).

The reason that pregnancy urine can be used to test for the gravid state is that the laboratory animal that is used is usually a rodent and in these animals the chorionic gonadotropic factor does stimulate follicular growth as well as development of the corpus luteum.

Reliable investigators have observed degenerative changes in the ovaries of women and monkeys who have received injections of chorionic gonadotropin.* It also exerts an effect on the interstitial cells of the testicle in the male, causing the formation of more male hormone (androgen) which in turn stimulates the growth of accessory sex organs.

Chorionic gonadotropin has been used for a variety of conditions, many times inadvisedly.

Uses.—

1. In the treatment of cryptorchidism (undescended testicle) when there is no anatomic obstruction to prevent testicular descent.

¹Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, 1941, p. 1186.

*N. N. R., 1947, p. 374.

respond well to estrogenic therapy. This is due to the fact that large doses of ovarian hormones depress the secretion of the gonadotropic hormones of the anterior pituitary. Vasomotor disturbances and headache can often be relieved. Symptoms which are of psychic origin do not respond to this type of therapy as a rule. The estrogenic substances may be administered orally, intravaginally, or parenterally. Both the dosage and the method of administration must be decided in relation to each individual patient.

2. In the treatment of gonorrheal vaginitis in children. This condition has been satisfactorily and successfully treated with estrogens. The basis of treatment lies in the fact that estrogenic substances cause the vaginal membrane to change to the adult type which is less easily invaded by pathogenic microorganisms. The epithelium thickens, and there is increased cornification of the top layers of epithelium as well as an increase in the amount of acidity which further inhibits bacterial growth. Administration of estrogenic substances is usually by means of a vaginal suppository. Therapy is expensive and has been replaced to some extent by the use of sulfonamides.

3. Suppositories containing estrogenic substances are also used in the treatment of senile vaginitis and pruritus vulvae.

Preparations.—

Estrone (Estronum) Theelin, U. S. P. A crystalline estrogenic substance obtained from the urine of pregnancy. Dosage: 1 mg. ($\frac{1}{60}$ gr.) in oil solution intramuscularly. For disturbance of menopause 0.2-1 mg. ($\frac{1}{300}$ - $\frac{1}{60}$ gr.) 2000-10,000 international units once or twice weekly. Larger doses 5 mg. (50,000 I.U.) per week for resistant kraurosis vulvae. Estrone is effective by mouth if dosage is adequate.*

Estriol, N. N. R. Theelol (Estriol and Theelol are nonproprietary synonyms). This is also a crystalline estrogenic substance obtained from the urine of pregnancy. When injected it is much less active than estrone. Dosage: 0.06-0.12 mg. ($\frac{1}{1000}$ - $\frac{1}{500}$ gr.) orally 1-4 times daily either alone or with parenteral therapy.

Estradiol Benzoate (Estradiolis Benzoas), U. S. P. Dosage: 1 mg. ($\frac{1}{60}$ gr.) orally or intramuscularly.

Estrogenic Substances, N. N. R., Amniotin (Squibb), (Water insoluble). A highly concentrated, noncrystalline preparation of estrone along with a small varying amount of other estrogenic ketones extracted from the urine of pregnant mares. Dosage:

*N. N. R., 1947, p. 342.

as the growth and distribution of hair, texture of the skin, and distribution of body fat, the character of the voice and the maintenance of these characteristics throughout adult life. The follicular hormone apparently exists not as an entity but as a number of related polymorphic forms which differ in their activity. This group of substances which exhibit similar estrogenic activity are called estrogens.¹ The group includes both the natural estrogens and synthetic substances which have similar effects in the body.

Sources.—Estrogenic substances are found in a variety of places and in both plants and animals. They are found in the blood of both sexes, in testicular fluid, feces, bile, placenta, and pregnancy urine of both human beings and mares. They vary somewhat chemically in accordance with the source from which they are obtained.

Action.—When injected into immature animals, estrogens are capable of hastening sexual maturity. This reaction is used in the standardization of extracts, especially the changes produced in the vaginal epithelium of rats.

Estrogenic substances are capable of relieving many of the symptoms of menopause and of producing changes in the castrate animal that are associated with estrus. They also increase contractility of uterine muscle and make it more sensitive to oxytocics like pituitrin.

Toxicity.—Long-continued administration of large doses of estrogens tends to produce sclerosis of the ovaries (Kunde, Leonard) and Moore says such doses injure the gonads because the production of gonad-stimulating and growth-stimulating hormones of the anterior pituitary are inhibited. Furthermore, it has been shown that large doses of estrogens disturb calcium metabolism in the body when given over a period of time.

Estrogens are carcinogenic when administered experimentally in animals which have an inherited sensitivity to mammary carcinoma.¹ Many clinicians believe that estrogens are therefore contraindicated in the treatment of women with a personal or family history of malignancy of the reproductive system.²

Therapeutic Uses.—

1. To relieve certain symptoms of menopause. At the time of menopause the normal endocrine balance is disturbed by the gradual cessation of ovarian function. The pituitary gland apparently attempts to compensate for the lack of ovarian activity by temporary hyperfunction. Symptoms caused by this compensatory reaction

¹Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, 1941, p. 1193.

²N. N. R., 1947, p. 333.

respond well to estrogenic therapy. This is due to the fact that large doses of ovarian hormones depress the secretion of the gonadotropic hormones of the anterior pituitary. Vasomotor disturbances and headache can often be relieved. Symptoms which are of psychic origin do not respond to this type of therapy as a rule. The estrogenic substances may be administered orally, intravaginally, or parenterally. Both the dosage and the method of administration must be decided in relation to each individual patient.

2. In the treatment of gonorrheal vaginitis in children. This condition has been satisfactorily and successfully treated with estrogens. The basis of treatment lies in the fact that estrogenic substances cause the vaginal membrane to change to the adult type which is less easily invaded by pathogenic microorganisms. The epithelium thickens, and there is increased cornification of the top layers of epithelium as well as an increase in the amount of acidity which further inhibits bacterial growth. Administration of estrogenic substances is usually by means of a vaginal suppository. Therapy is expensive and has been replaced to some extent by the use of sulfonamides.

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Estradiol Benzoate (Estradiolis Benzoas), U. S. P. Dosage: 1 mg. ($\frac{1}{60}$ gr.) orally or intramuscularly.

Estrogenic Substances, N. N. R., Amniotin (Squibb), (Water insoluble). A highly concentrated, noncrystalline preparation of estrone along with a small varying amount of other estrogenic ketones extracted from the urine of pregnant mares. Dosage:

*N. N. R., 1947, p 342.

2000-20,000 international units injected one or more times weekly. Suppositories of this substance are used in senile vaginitis. For gonorrheal vaginitis in children 1000-2000 international units in glycerogelatin suppositories may be given daily. This may be supplemented by small doses of the oil solution if necessary. Preparations in capsule form may be used to supplement parenteral therapy.

Estrogenic Substances, N. N. R. (Premarin—Ayerst), Water soluble
A preparation of mixed estrogens from the urine of pregnant mares. The principal estrogen present is sodium estrone sulfate.

Water-soluble estrogenic substances are used for the same conditions for which other estrogenic substances are employed. Dosage: 1.25 mg. daily is usually sufficient to control menopausal symptoms. Senile vaginitis and pruritis vulvae are usually relieved with doses of between 1.25 and 3.75 mg.

Diethylstilbestrol (Stilbestrol), U. S. P. A relatively simple and cheap synthetic estrogenic substance which duplicates practically all known actions of the natural estrogens. It is relatively active by mouth as well as parenterally. Nausea, vomiting, headache, and dizziness are side reactions which may accompany its therapeutic use. These symptoms are associated with rapid absorption and are less commonly seen when preparations are given which are more slowly absorbed.¹ Diethylstilbestrol is not significantly more toxic, however, than the natural estrogens.² None the less, patients receiving the drug should be under medical supervision.

The average dose for treatment of menopausal symptoms is 0.5 to 1.0 mg. daily by mouth or smaller dosage by injection.

Diethylstilbestrol Capsules (Capsulae Diethylstilbestrolis), U. S. P.
Dosage: 0.5 mg. ($\frac{1}{120}$ gr.).

Diethylstilbestrol Injection (Injectio Diethylstilbestrolis), U. S. P.
Dosage: 0.5 mg. ($\frac{1}{120}$ gr.) intramuscularly.

Diethylstilbestrol Tablets (Tabellae Diethylstilbestrolis), U. S. P.
Dosage: 0.5 mg. ($\frac{1}{120}$ gr.).

Ointments or suppositories may be used for topical application, especially for senile vaginitis, kraurosis vulvae, and gonorrheal vaginitis in children. Dosage of all preparations should be kept at the minimum necessary for relief of symptoms.

Hexestrol, N. N. R. (dihydrodiethylstilbestrol), is another synthetic estrogenic substance. It is reported to be less toxic than diethyl-

¹Report of the Council on Pharmacy and Chemistry, J. A. M. A. 119: 634, 1942.
²N. N. R., 1947, p. 348.

stilbestrol. It is effective when given by mouth and is used for much the same conditions as diethylstilbestrol.¹ Its therapeutic status is not fully determined.

Benzestrol, N. N. R., is a synthetic estrogen which is not chemically related to stilbestrol. It is reported to be relatively nontoxic, and it has been found effective in the treatment of distressing menopausal symptoms. The average oral dose is 2 or 3 mg. daily and the parenteral dose is from 2 to 5 mg. Adjustments in dosage must be determined according to clinical observation and individual needs.

LUTEAL HORMONE

The luteal hormone functions in the preparation and maintenance of the lining of the uterus for the implantation and nourishment of the embryo. It supplements the action of the follicular hormone in the action on the uterus and also in the mammary glands. It suppresses ovulation during pregnancy and keeps the uterus in a quiescent state by inhibiting irritability of the uterine muscle.

Progesterone is closely related chemically to both testicular and estrogenic hormones. It is prepared commercially by oxidizing cholesterol. The greater part of progesterone that is excreted into the urine is in the form of pregnanediol which is physiologically inactive.¹

Therapeutic Uses.—

1. In cases of threatened abortion, the administration of luteal hormone may maintain the uterus in a proper state of nutrition and relaxation.
2. For the relief of dysmenorrhea, which may be due to hypermotility of the uterus.
3. In cases of metrorrhagia or menorrhagia the administration of luteal hormone is sometimes helpful.

Preparations.—The luteal hormones do not have an official status. *Progestin* is a preparation on the market and is a crude extract of ovarian tissue. *Progesterone* is a synthetic preparation of pure crystalline hormone. *Pregneninolone* is a substance closely related to progesterone and is found in pregnancy urine. It is apparently effective in tissues that have not been previously primed by an estrogen.² It is said to be effective in stimulating the sex glands of the

¹Davison, F. R.: *Synopsis of Materia Medica, Toxicology, and Pharmacology*, 1944, p. 641.

²Davison, F. R.: *Synopsis of Materia Medica, Toxicology and Pharmacology*, p. 642.

male as well as having progestational activity in the female, and can be given by mouth.

All of the above preparations can be obtained in oil solution for intramuscular injection. Progesterone is not effective except by parenteral administration.

Male Sex Hormones

Testosterone Propionate, U. S. P.—Normal development and maintenance of male sex characters depend on adequate amounts of the male sex hormones which are termed androgens.

One hormone called testosterone is related chemically to progesterone. Testosterone is believed to be the true testicular hormone and androsterone is a related substance which is excreted in the urine of males.

The androgens function in the development and maintenance of normal states in the sex organs. Administration to immature males causes growth of the sex organs and the appearance of the secondary sex characters. When a high concentration of androgenic substance is maintained in the circulation, anterior pituitary action is inhibited and spermatogenesis is retarded.

In mammals both sexes form both the male and the female hormones although they are antagonistic to each other. The administration of testosterone can suppress menstruation and cause atrophy of the endometrium.

Therapeutic Uses.—Androgens have been used in replacement therapy for patients with hypogonadism and in prepuberal and postpuberal castrates. It produces marked changes in sex organs, body contour, and voice, provided the deficiency state has not been present too long. Androgens have little effect in senile men and in patients with psychic impotence, or as an aphrodisiac.¹

Alone or with gonadotropic substances, androgens have been employed in the treatment of cryptorchidism. They have also been used in the treatment of dysmenorrhea, menopausal states, and other gynecologic conditions. Favorable results have been reported for its use in relief of subjective symptoms associated with the male climacteric just as estrogens are of value in relieving symptoms of similar origin in women.

Testosterone Propionate has been administered in the treatment of bone metastasis secondary to carcinoma of the female breast. However, there are insufficient data to determine whether the im-

¹Davison, F. R.: *Synopsis of Materia Medica, Toxicology and Pharmacology*, p. 645.

provement which is sometimes seen is of a permanent nature and which type of carcinoma is most sensitive to this hormone. The use of small amounts has been recommended in the treatment of menstrual disorders and larger doses for carcinoma of the ovaries, but the present evidence of its usefulness is inconclusive.

Administration.—Testosterone Propionate is usually given parenterally (intramuscularly) in oil. It has a standard potency of 50 international capon units per milligram. The dosage must be regulated according to the response obtained and the effect desired. Maximum effects are said to be obtained from 25 mg. three times a week but as little as 5 mg. three times a week may be sufficient to relieve constitutional symptoms.

Caution should be observed to prevent noticeable loss of feminine characteristics in women (deepening of the voice, growth of hair on the face, etc.) or precocious sexual development in young boys. The preparation has no value in the treatment of sterility in the male or impotence which is not of glandular origin.

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UNIT XI

CHAPTER XX

CHEMOTHERAPY OF SPECIFIC DISEASES

Chemotherapy means the treatment of infectious diseases by the use of chemicals which kill the causative microorganisms but produce little or no injury in the patient. Antiseptics and disinfectants are chemotherapeutic agents which act locally to inhibit or kill microorganisms. In this chapter the chemotherapeutic agents which act systemically—systemic anti-infectives—will be discussed.

Until recently chemicals used to kill pathogenic protozoa and closely related organisms were much more successful than the chemicals used against bacteria. Thus we find that systemic chemotherapy has been used against the organisms causing malaria, syphilis, and amebiasis for many years. Not until sulfanilamide was introduced in 1935 was there a really effective chemical against the pneumococcus, meningococcus, streptococcus, and many other bacteria.

MALARIA

Malaria is the most prevalent of all diseases in spite of efforts to control the causative organisms and their insect vectors. The organisms which cause this disease are protozoa called *Plasmodium vivax* or tertian parasite, *Plasmodium malariae* or quartan parasite, and *Plasmodium falciparum* or estivo-autumnal parasite. Each of these causes a different type of malaria. The malaria parasites undergo two phases of development: the sexual cycle which takes place in the mosquito and the asexual cycle which occurs in the human body. The mosquito which bites an infected human being ingests the asexual forms known as schizonts and the sexual forms known as gametocytes. In the mosquito the asexual forms are destroyed, but the female gametocyte is fertilized by the male, and development into asexual forms results. These are introduced into the blood of human beings by the bite of the *Anopheles* mosquito.

The asexual cycle of the parasite in the human being is as follows: The asexual form, the schizont, enters a red blood cell where it grows and matures and then subdivides into 15 or 20 sporelike bodies called merozoites. The red blood cell ruptures and sets free

the merozoites, each of which can then penetrate another red blood cell and undergo the same process. The recurring chills and fever which are the main clinical symptoms of malaria occur when the red blood cells break up and release the young parasites.

The sexual cycle of the parasite is as follows: Some of the asexual forms in the human being develop into sexual forms—the male and female gametocytes. The sexual forms do not cause any symptoms and fertilization does not take place in the human being. When the *Anopheles* mosquito bites an infected person and ingests the gametocytes, fertilization of the female by the male takes place. The fertilized cell develops into a number of asexual forms which cause no harm in the mosquito. The asexual forms when injected into the blood of human beings by the mosquito's bite undergo the asexual cycle described in the preceding paragraph. Persons who harbor the sexual forms are called carriers because the mosquito can receive the sexual forms from them.

Thus it is the schizonts (asexual forms) which cause the clinical symptoms of malaria, but the gametocytes which make a person dangerous as a carrier.

Quinine

Cinchona bark is the source of quinine, the alkaloid which is specific in treating malaria. The cinchona trees are indigenous to South America, but because of the great demand for quinine they have been introduced into the East Indies, Jamaica, Java, and other countries. Cinchona was introduced into Europe in 1640 and received its name from the Countess Cinchon, wife of the Peruvian Viceroy, who was cured of a fever by it. Before the beginning of World War II, about 90 per cent of the world's supply of cinchona was produced by the Dutch, mainly in Java. After the fall of the Dutch East Indies in 1942 the Allied countries were cut off from their usual supply, making it necessary for the Allies to rely on synthetic drugs for the control of malaria in troops fighting in the tropics. The use of atabrine, which was known before World War II, has thus been increased tremendously. In May, 1944, it was announced that quinine had been synthesized by Woodward and Doering. The synthesis of quinine is too new for us to know whether it will become a commercial method or remain a laboratory procedure.

The most important alkaloids belonging to the cinchona group are quinine and quinidine. The latter is discussed in the chapter

on heart depressants. In addition to these, about 20 other alkaloids have been isolated from cinchona bark.

Main Action of Quinine.—

1. Quinine acts as a selective malarial parasiticide. Quinine is a general protoplasmic poison. In sufficient concentrations it is fatal to all cells. It affects protozoa more than bacteria. In therapeutic doses it is particularly effective against the Plasmodia causing malaria.

2. Quinine acts as an antipyretic and analgesic. Quinine acts as an antipyretic by resetting the hypothalamus for normal temperature. It acts as an analgesic by depression of the optic thalami. These actions are similar to that of the salicylates but compared with the salicylates the antipyretic action is slower and the analgesic action is not as effective.

3. Quinine is irritating locally. When taken orally, large doses cause nausea, vomiting, and diarrhea. When injected intramuscularly, it is likely to cause abscesses. When injected intravenously, it causes irritation of the intima which may result in thrombosis.

4. Quinine stimulates contractions of uterine muscles. Its action is not as reliable as other uterine stimulants such as ergot and pituitrin.

5. Quinine acts as an appetizer in small doses because of its bitter taste.

Uses of Quinine.—

1. Quinine is used chiefly as a specific in malaria. It is effective in suppressing and treating clinical attacks of malaria because it kills the schizonts (asexual forms) of all types of malaria parasites. It is not effective against the gametocytes (sexual forms) of *Plasmodium falciparum*. Relapses of malaria may occur, but the earlier the treatment the less common the relapses.

Quinine may be administered for malaria as follows:

a. *For suppressive treatment:* Quinine sulfate 0.6 Gm. (10 gr.) daily. By suppressive treatment is meant the emergency type of administration as used in the army which prevents development of clinical symptoms though not the infection.¹

b. *For treatment of clinical attacks:* Quinine sulfate 1 Gm. (15 gr.) by mouth three times a day after meals for two days, then 0.6 Gm. (10 gr.) three times a day after meals for five days.¹

2. In fever it is used as an antipyretic.

¹The Drug Treatment of Malaria, Suppressive and Clinical. Circular Letter No. 153, Office of the Surgeon General, U. S. Army, J.A.M.A. 123: 205 (Sept. 25), 1943

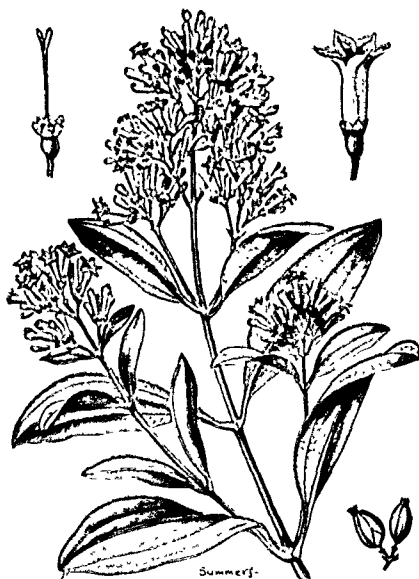


PLATE XV—*Cinchona calisaya* (Peruvian bark) (From Jackson.
Experimental Pharmacology and Materia Medica)



3. It is used as an analgesic for joint and muscle pain and for headaches.

4. Quinine dihydrochloride and urethane, 5-10 per cent solutions, are used as a sclerosing agent in the treatment of varicose veins. It causes a slough if it gets outside the vein. Other drugs such as sodium morrhuate, which do not cause sloughing when they get outside the veins, are preferred as sclerosing agents.

5. It is occasionally used to initiate labor or increase labor pains.

6. It is occasionally given to improve appetite (see Bitters, page 238).

Poisoning or Cinchonism.—Symptoms of a mild poisoning are ringing in the ears, headache, nausea, dizziness, and slightly disturbed vision. More pronounced toxicity will cause symptoms of the gastrointestinal tract, skin, nervous system, and cardiovascular system. Delirium, coma; low blood pressure, and shallow respirations occur terminally.

The treatment must suit the symptoms. Mild poisoning usually subsides when the medication is discontinued. In the more severe forms body temperature must be maintained, respiratory stimulants given as indicated, and a stomach lavage performed if the fairly insoluble salts have been ingested.

Administration.—For malaria, the oral administration of quinine salts is the preferred method. When oral administration is not feasible, quinine derivatives may be given intravenously, but this method should be used only for emergencies, and the injection should be made slowly, for a dangerous lowering of the blood pressure usually occurs.

Preparations.—

Quinine (Quinina), N. F. Dose: 1 Gm. (15 gr.).

Quinine Sulfate (Quininae Sulfas), U. S. P. Dose: 0.6 Gm. (10 gr.).

Quinine Bisulfate (Quininae Bisulfas), U. S. P. Dose: 1 Gm. (15 gr.).

Quinine Dihydrochloride (Quininae Dihydrochloridum), U. S. P. Dose: 1 Gm. (15 gr.). By intravenous or intramuscular injection 0.3 Gm. to 0.6 Gm. (5-10 gr.).

Quinine and Urethane Injection, U. S. P. For use as a sclerosing agent to obliterate varicose veins. Average dose at one site is 1 cc. Total quantity injected at a single time should not exceed 5 cc.

Totaquine (Totaquina), U. S. P. A mixture of alkaloids from bark of cinchona containing not less than 70 per cent of the total crys-

tallizable alkaloids. It is used in the treatment of malaria in the same manner as the quinine compounds. Dose: 0.6 Gm. (10 gr.).

Quinacrine Hydrochloride, U. S. P. (Atabrine)

Atabrine is the trade name for the synthetic drug of the acridine dye series which is used in the treatment of malaria. It is yellow in color. "Available evidence indicates that atabrine is as effective as quinine (or more so) both in suppressive use and in the treatment of clinical attacks. No available drug or plan of administration can be expected to prevent relapses in all cases. . . ."

Action.—The action of atabrine resembles that of quinine in that it is effective against the schizonts (asexual forms) of all types of malaria parasites so that it will cure the clinical attacks of the disease. It is not effective against the gametocytes (sexual forms) of *Plasmodium falciparum* but is effective against the gametocytes of the other types of Plasmodia. Atabrine does not stimulate the uterine muscles and so can be used during pregnancy.

Toxic Symptoms.—The toxic symptoms are nearly always mild and consist of nausea, abdominal cramps, occasional headache, vomiting, and diarrhea. Giving soda bicarbonate or sweetened drinks such as tea usually prevents these reactions which are never serious. About one-third of those taking atabrine develop a yellow color in the skin which is due to the dye appearing in the skin. This disappears a few weeks after the drug has been discontinued and is not an indication for stopping the drug.

Administration.—For suppressive treatment the following method is used: Atabrine 0.1 Gm. (1½ gr.) is given once a day six days a week.¹

For treatment of clinical attacks the following is an example of a method used: Atabrine 0.2 Gm. (3 gr.) and soda bicarbonate 1 Gm. (15 gr.) by mouth with 200 to 300 cc. of water (or an equal amount of sweetened tea or fruit juice) every six hours for five doses. This is followed by a maintenance dose of 0.1 Gm. (1½ gr.) three times a day for six days. The reason for giving the large initial doses followed by the small maintenance doses is that atabrine is localized first in the tissues and then later in the blood plasma and so effective plasma concentrations are reached quickly by the above method.¹

Atabrine dihydrochloride 0.2 Gm. (3 gr.) in 5 cc. of sterile distilled water may be injected intramuscularly into each buttock, but the oral method is preferred.

¹Ibid. (see page 404).

Preparation.—

Quinacrine Hydrochloride (*Quinacrinae Hydrochloridum*), U. S. P. (Atabrine). Dose: 0.1 Gm. ($1\frac{1}{2}$ gr.).

Pamaquine Naphthoate, N. F. (Plasmochin)

Plasmochin is a synthetic quinine substitute, the chemical formula of which is very much like that of quinine.

Action.—Plasmochin is especially effective against the gametocytes or sexual forms of the *Plasmodium falciparum*, against which quinine and atabrine are not very effective. Thus it is an important agent in preventing the transmission of this organism which causes estivo-autumnal malaria.

It is not used for the treatment of clinical attacks of malaria because safe doses have little effect on schizonts.¹ If used for clinical attacks it is not effective alone but must be used with other drugs. It may be given with quinine or following treatment with atabrine (not with atabrine).

Toxic Symptoms.—Plasmochin is likely to cause toxic symptoms because the margin of safety between therapeutic and toxic doses is small. The patient must be closely observed and the drug discontinued as soon as toxic symptoms appear. The most important symptoms are: headache, dizziness, abdominal pain, nausea, vomiting, drowsiness, and cyanosis. Hemoglobinuria, jaundice, and acute yellow atrophy of the liver are rarer but very dangerous.

Administration.—An example of a method used is: Plasmochin 0.01 Gm. ($\frac{1}{8}$ gr.) by mouth three times a day following meals. Each dose is accompanied by 1 Gm. (15 gr.) of soda bicarbonate. Fluid and sugar intake should be liberal during and for some days after.¹

Preparation.—

Pamaquine Naphthoate (*Pamaquinae Naphthoas*), N. F. (Plasmochin). Dose: 20 mg. ($\frac{1}{2}$ gr.).

CHEMOTHERAPY OF SYPHILIS

Syphilis became known in Europe shortly after the return of Columbus from Haiti in 1493. The treatment was for a long time empirical. It could not be otherwise until 1905, when Schaudinn discovered the causative spirochete in the lesions.

¹Ibid. (see page 404).

Syphilis is an infectious disease caused by the *Treponema pallidum*. Its course may be divided into three stages, characterized by very definite symptoms. The first symptom is the formation of an ulcer, called the chancre, at the point where the germ enters the body. In the second stage, the most important symptoms are a skin rash, white patches in the mouth, and swelling of all the lymph glands. The third stage or late syphilis may follow immediately or may not appear for several years. It is characterized by formation of tumors, or gummas, which may develop on any organ of the body. This stage includes hepatic syphilis, neurosyphilis, cardiovascular syphilis, and syphilis of bones.

The following list summarizes some of the chief antisyphilitic drugs now being used:

1. To kill the *Treponema pallidum*
 - a. Arsenicals

Most active in killing *Treponema pallidum*
 - b. Bismuth compounds

Less active than the arsenicals
More active than the mercurials
 - c. Mercurials

Less active than the arsenicals and bismuth
 - d. Penicillin

Too new to be assured of a definite place as yet in the therapy of syphilis but recent trials are very promising
2. To dissolve gummas of the third stage of syphilis

Iodides

Arsenic in Syphilis

While arsenic was known to the ancients it was considered by them to be a kind of sulfur. Aristotle mentions it. Theophrastus called it *arsenikon*, meaning "potent." Arsenic trioxide has been used in medicine since the beginning of the Christian era. Dioscorides (second century A.D.) recommended As_2S_3 as a caustic and depilatory, etc.

In European medicine, compounds of arsenic were limited to internal use until the end of the seventeenth century. Some decades later a paste of arsenous acid was used in the treatment of cancer of the skin. The employment of arsenic in the treatment of protozoal diseases was first suggested by the famous African explorer David Livingstone (1858). He recommended it for the treatment of the trypanosome disease caused by the tsetse fly in animals.

Bruce, in 1894, discovered a trypanosome in the blood of infected animals, and in 1895 discovered a treatment of tsetse fly infections of animals. Ehrlich and Shiga (1904) studied the effect of atoxyl on trypanosomes in vitro.

Atoxyl was the first organic arsenic compound employed in experimental trypanosomiasis, by Thomas, of Liverpool, in 1905, who found it superior to inorganic

arsenic. Ehrlich, hearing of the work of Thomas, became interested, and his work led to the development of "606" or salvarsan (1905), which in time led to the discovery of sulfarsphenamine by Voegtlin and Johnson in 1922; and stovarsol (acetarsone, N. N. R.), or "Fournéau 309" by Fournéau and Levaditi in 1921, and of tryparsamide by Jacobs and Heidelberger, 1919.

Arsphenamine

Arsphenamine, U. S. P., or Salvarsan is a complex organic, arsenic salt containing not less than 30 per cent of arsenic. It is a yellow, crystalline powder which oxidizes readily upon exposure to air, becoming darker in color and more toxic. It is soluble in water, but since the solution is strongly acid in reaction it must be made alkaline before it is used.

Action and Uses.—Arsphenamine is a specific for syphilis in all stages, but is especially effective in the primary stage, soon relieving all the symptoms. Months of continuous treatment are necessary to control syphilis under usual methods of treatment.

Arsphenamine is given with good results in various other diseases, such as relapsing fever and Vincent's angina, which are caused by spirochetes.

Administration and Dosage.—The dose of arsphenamine ranges from 0.3 to 0.6 Gm. (5 to 10 grains). The drug is given intravenously.

Because of its instability in air, arsphenamine is sold in nitrogen-filled or vacuum-sealed ampules, each containing a dose of the desired amount. These should be kept in a cool place. The tubes should be immersed in alcohol for fifteen minutes before opening to detect any possible leak. For intravenous injection a clear, alkaline solution is used, which is prepared in some such manner as the following: For each 0.1 Gm. of arsphenamine required as determined by the patient's weight, 2 cc. of sterile freshly distilled water are used. The powder is dissolved thoroughly and to this solution is added 0.9 cc. of normal sodium hydroxide solution for each 0.1 Gm. of acid arsphenamine and sterile water to 30 cc. The solution should be used thirty minutes to one hour after preparation and under no circumstances should any powder from a previously opened tube be employed.

The standard method of administering arsphenamine is to give it in courses of one injection weekly for six to eight weeks, alternating without rest periods with courses of bismuth or mercury. These courses are continued for from one to one and a half years or until the symptoms have disappeared and blood tests are negative.

Neoarsphenamine

Neoarsphenamine, U. S. P., or Neosalvarsan is a preparation containing not less than 19 per cent of arsenic. It resembles arsphenamine closely in appearance and other properties but differs from it in yielding a solution which is neutral so that it does not need to be neutralized. It also differs from arsphenamine in that it must be injected immediately after preparation.

Action and Uses.—The actions and uses of neoarsphenamine are practically the same as those of salvarsan.

Administration.—Because of its instability, neoarsphenamine is sold in ampules or tubes, each of which contains a dose ranging from 0.1 to 0.9 Gm. ($1\frac{1}{2}$ to $13\frac{3}{10}$ grains). The average dose is 0.45 Gm. (7 grains). The powder should be dissolved in cold sterile distilled water, using 2 cc. of water to 0.1 Gm. of drug, and the solution should be injected at once since neoarsphenamine oxidizes rapidly and becomes toxic. The injection should be made very slowly, at least five minutes being allowed for the procedure.

Sulfarsphenamine

Sulfarsphenamine, U. S. P., is a compound of sulfur and arsphenamine, containing not less than 19 per cent of arsenic. It is an orange yellow powder having an odor resembling that of sulfur dioxide and arsine. It dissolves readily in water, yielding a yellow solution which is acid to litmus.

Action and Uses.—The actions of sulfarsphenamine are similar to those of neoarsphenamine but sulfarsphenamine has a high incidence of late toxic reactions in adults. One advantage of it is that it can be given intramuscularly and so it has been used in infants and in obese patients in whom intravenous injection is difficult. Because it is so toxic it should not be used when other safer drugs can be used.

Administration.—The average dose of sulfarsphenamine is 0.4 Gm. (7 grains). For intramuscular use, the powder is dissolved in sterile, freshly distilled water in the proportion of 0.1 Gm. to 0.3 cc. ($1\frac{1}{2}$ grains to 5 minims).

Oxophenarsine Hydrochloride, U. S. P.

Oxophenarsine Hydrochloride (Mapharsen—Parke, Davis) is a trivalent arsenical which contains approximately 31 per cent arsenic. It is not an arsphenamine but an oxidation product of arsphenamine. It is used in the treatment of syphilis and is claimed to have a rapidly beneficial effect, particularly in early syphilis.

It, which has been used clinically since 1932, is very popular at present. For example, in 1942 the United States Army altered the scheme of treatment of syphilis formerly used and this preparation was recommended to the exclusion of other arsenicals. The advantages of Oxophenarsine Hydrochloride are: (1) It is less toxic than arsphenamine and neoarsphenamine, (2) many patients who cannot tolerate the arsphenamines can usually tolerate Oxophenarsine Hydrochloride, and (3) nitritoid crises do not occur with it. In addition, it is easier to administer; it does not need to be alkalized; it can be injected immediately or hours after it is prepared, and it can be rapidly administered.

Dosage and Administration.—The initial intravenous dose is 0.03 Gm. for women and 0.04 Gm. for men. The dose may be increased for second injection to 0.04 Gm. and 0.06 Gm., respectively. Because of rapid excretion the injections may be given every four or five days. The dosage is considerably less than that of the arsphenamines and the danger of arsenic poisoning is therefore less. The standard treatment for syphilis consists of courses of ten weekly injections alternating without rest periods with courses of heavy metals.

Tryparsamide

Tryparsamide, U. S. P., is not an arsphenamine but an arsenical which is given primarily in the treatment of central nervous system syphilis. Many patients with paresis improve with its use. The chemical is highly effective for trypanosomes but relatively feeble in its action on treponema. It is said to be able to penetrate tissues very well, which would explain its action in neurosyphilis.

The drug is usually given intravenously in doses ranging from one to three grams. The weekly injections may be given over a period of eight to sixteen weeks. Because it can cause optic nerve injury leading to blindness, it should be given with care.

Acetarzone (Stovarsol)

Acetarzone, N. F., is an organic pentavalent arsenical which has been used not only in the treatment of syphilis, but also for amebiasis. It has an advantage in that it may be given orally and so it has been used for the treatment of congenital syphilis in children. Its use, however, is accompanied by a rather high level of toxicity which, combined with the rather poor results obtained, make it an undesirable drug to use for syphilis.

Toxic Reactions to the Organic Arsenicals.—

1. *Nitritoid Crisis*.—This reaction is so named because the symptoms resemble those following administration of nitrites. It occurs during or immediately after the injection and the symptoms include a sense of fullness in the head, flushed skin, fall in blood pressure, severe pain in the back, and vomiting. Sometimes death occurs in severe cases. The treatment is to give epinephrine.

2. *The Jarish-Herxheimer Reaction*.—This consists of a febrile response with a flare-up of lesions on skin and mucous membranes. It follows the first injection of arsphenamines and is thought to be due to a releasing of toxins from the organisms which are killed by the first dose. The general reaction usually occurs a few hours after the drug is given. The intensification of lesions occurs within one or two days. No treatment is necessary, though the reaction should be explained to the patient in order to allay anxiety.

3. *Late Reactions*.—These occur a few days after the injection and usually are more serious than the first two described. The symptoms vary and may consist of dermatitis, jaundice, blood dyscrasias, and nervous system symptoms.

Arsenic Preparations.—

Arsphenamine (Arsphenamina), U. S. P. (Salvarsan). Dose: Intravenous, 0.3 Gm. (5 gr.).

Neoarsphenamine (Neoarsphenamina), U. S. P. (Neosalvarsan). Dose: Intravenous, 0.45 Gm. (7 gr.).

Sulfarsphenamine (Sulfarsphenamina), U. S. P. Dose: Intramuscular 0.45 Gm. (7 gr.).

Oxophenarsine Hydrochloride, U. S. P. Dose: Intravenous, 0.03 Gm. for women and 0.04 Gm. for men, initially. (Maximum dose may be regarded as 0.06 Gm. to 0.07 Gm.)

Tryparsamide (Tryparsamidum), U. S. P. Dose: Intravenous, 2 Gm. (30 gr.).

Acetarson (Stovarsol), N. F. Dose: 0.25 Gm. for adults.

Bismuth

Bismuth is less effective than the arsenicals but more effective and less toxic than the mercurials in the treatment of syphilis.

Bismuth Preparations.—There are a good many bismuth preparations accepted by U. S. P. and N. N. R. as antisypilitics. Some are soluble and are dissolved in water or oil; some are insoluble and are suspended in water or oil. The insoluble preparations are injected once a week while the soluble preparations must be injected

every two or three days to maintain effective amounts in the body. This is an advantage of the insoluble preparations. There is not complete agreement as to which type of preparation is better, some syphilologists preferring one type and some the other. Recently a preparation called Sobisminol Mass, which can be given orally, has been used with promising results.

Representative bismuth preparations are:

1. *For intramuscular use:*

- a) Bismuth Subsalicylate (Bismuthi Subsalicylas), U. S. P.

This is a suspension in oil. It is injected intramuscularly in 0.1 Gm. (1½ gr.) doses.

- b) Bismuth Potassium Tartrate (Bismuthi Potassii Tartras), U. S. P.

Dosage:

- a) Oily suspension—from 0.1 to 0.2 Gm. by intramuscular injection at intervals of 7 days.
b) Aqueous Isotonic solution—50 mg. by intramuscular injection three times a week.

2. *For oral use:*

Sobisminol Mass, N. N. R. The dose is 2 or 3 capsules three times a day taken with plenty of water. Each capsule contains 150 mg. of metallic bismuth.

TOXIC SYMPTOMS.—These are not common. The following should be watched for: stomatitis, blue line on gums, albumin or casts in the urine, and skin reactions. Good oral hygiene helps prevent stomatitis.

Mercury

Next to the precious metals, mercury held the highest place in the medieval laboratories. The actual date of its discovery is uncertain, but it was known in the time of Aristotle. Sudoff says that mercuric unctions were used for leprosy, chronic eczema, and skin eruptions in the twelfth century, and at the end of the fifteenth century they were used in the treatment of syphilis. Until the discovery of arsphenamine in 1905, mercury held first place in the treatment of syphilis, and it is still used as an adjunct in the treatment.

Mercury is more poisonous than bismuth and is inferior to bismuth in the treatment of syphilis. Therefore the use of arsenicals and bismuth in alternating courses is better than the use of arsenicals and mercury. Under certain circumstances mercury may be substituted for bismuth, but the latter should be used whenever possible.

Administration, Preparations and Doses.—

1. *By intramuscular injection.*—The preparations are of two types: soluble and insoluble mercury salts. Examples of preparations given intramuscularly are:

Mercuric Salicylate (*Hydrargyri Salicylas*), N. F. This is a sterile suspension of insoluble mercuric salicylate in oil. The dose is 0.1 Gm. ($1\frac{1}{2}$ gr.) once a week.

Mercuric Succinimide (*Hydrargyri Succinimidum*), N. F. Dose: 15 mg. ($\frac{1}{4}$ grain) daily or every other day. This is a preparation which is soluble in water and is more absorbable than the salicylate and so must be given more often.

2. *By inunction.*—Strong Mercurial Ointment (*Unguentum Hydrargyri Forte*), U. S. P., 4 Gm. (60 gr.) daily. This contains about 50 per cent of mercury in wool fat, white wax, and white petrolatum. The patient is instructed to rub in the ointment for 30 minutes at a different site each night. The site should be cleansed the morning following the application. The ointment may be diluted with equal parts of hydrous wool fat if it proves to be irritating. A course of mercury usually consists of daily applications for from six to ten weeks. There is also a Mild Mercurial Ointment, U. S. P., which contains about 10 per cent of mercury.

3. *Orally.*—In rare instances, as in old people, mercury is given orally for syphilis.

4. *By intravenous injection.*—This type of administration may be used but it is not popular in the United States. Mercury cyanide and oxycyanide are preparations used intravenously.

Iodine and the Iodides in Syphilis

Iodine was discovered in, and isolated from, the seaweed, *varec* or *kelp*. During stormy months in spring seaweeds are washed onto the coasts of Ireland, Scotland, and France. The inhabitants gather these and burn them in large heaps at as low temperatures as possible. The ash thus obtained is called *kelp* in Scotland and *varec* in Normandy (Mellor). This ash contains iodides from which iodine may be obtained (0.1 to 0.3 per cent). Some years after its discovery, its therapeutic powers were tried, and having been found valuable, it has been used ever since. In 1820 it was employed for the cure of goiter by Coindet, of Geneva. He found that enlarged glands and ulcers were benefited by it. This suggested its use in the treatment of syphilis.

Iodides.—The iodides are probably the most frequently used of all inorganic salts. The preparations commonly employed are: Potassium iodide, U. S. P., and Sodium iodide, U. S. P.

These salts are both very soluble in water and are usually given well diluted by mouth. The dose varies in nonsyphilitic cases from 0.3 to 2 Gm. (5 to 30 grains). In the treatment of syphilis, doses up to 5 Gm. or more may be given.

Action and Uses.—The chief use of iodides is in the treatment of the third stage of syphilis. They do not kill the germ of this disease and are of no use in recent syphilis. It is in later stages when gummatous exudates have formed that the iodides are of value. The mechanism of their action is not clearly understood. They break down the gummas and promote their absorption. They have a similar absorptive action on the lesions occurring in actinomycosis and blastomycosis. They should be given over a long period and in as large amounts as the patient can tolerate.

Iodides have been used to increase bronchial secretion in bronchitis, to promote the elimination of mercury and lead, and to prevent simple goiter.

Poisoning with iodides does not often occur, but long-continued use may cause unpleasant symptoms called "Iodism." The eyes are reddened and the flow of tears is excessive, the throat is sore and there is profuse secretion of saliva and bronchial mucus. Usually there is some cough and a slight fever. Skin eruptions may occur as in bromism, but they do not occur frequently.

Treatment.—When the administration of the iodides is discontinued, the symptoms soon disappear.

Preparations.—

Potassium Iodide (Potassii Iodidum), U. S. P. Dose: 0.3 Gm. (5 gr.).

Sodium Iodide (Sodii Iodidum), U. S. P. Dose: 0.3 Gm. (5 gr.).

Penicillin in Syphilis

Recent reports indicate that penicillin is very effective in treating syphilis, but this use is relatively new and it is difficult to evaluate the true place of penicillin in syphilotherapy. Penicillin is discussed in detail later in this chapter.

SUMMARY OF THE TREATMENT OF SYPHILIS

The present-day conservative treatment of syphilis consists mainly of alternating (or in the case of bismuth, overlapping) courses of weekly injections of arsenicals and a heavy metal—preferably bismuth. The arsenicals most commonly used are mapharsen and neosalvarsan. The most popular bismuth preparations are those which are not too rapidly absorbed as bismuth salicylate in oil, so that weekly injection is possible. The drug courses last approximately

ten weeks and are given without rest between them. Some doctors give iodides by mouth daily during the bismuth courses. The treatment continues for a year or a year and a half or as long as is indicated by the blood and spinal fluid reactions.

Massive or Intensive treatment of syphilis.—In recent years new methods of giving large doses of arsenicals in short periods of time have been tried. In general, the greater the dose, the greater the risk to the patient. The conservative treatment summarized in the preceding paragraph is considered the safest. Because it is difficult to get patients to continue the long treatment these newer methods are receiving considerable attention. Examples of semi-intensive and intensive treatments are as follows:

The Army plan which covers a period of twenty-six weeks and consists of alternating overlapping injections of mapharsen twice weekly and bismuth once weekly. This plan gives, in twenty-six weeks, amounts of mapharsen which would require more than a year to give by the conservative method of treatment.

The five-day drip method which consists in giving approximately 240 mg. of mapharsen in 5 per cent dextrose by intravenous drip for eight to twelve hours daily for five days, the total dose being about 1200 mg. Bismuth is sometimes given with this method.

There are other modifications, such as the 10-day method, etc. The shortest method is the one-day treatment in which fever therapy and mapharsen are combined. In this method, 0.25 gram of bismuth is given twenty-four hours before treatment. Then a five- to ten-hour fever therapy at 105°-106° F. is given and 120-240 mg. of mapharsen are given intravenously at the height of the fever.

It should be emphasized that the more intensive the method of treatment, the greater the percentage of deaths. Therefore, at present the newer methods should be used with great care and the conservative method should be the standard method of treatment in spite of articles in popular magazines which lead the public to believe that quick cures are easily accomplished.

Antimony

Antimony is used in the treatment of certain worm infestations notably schistosomiasis and filariasis. It is also used to treat leishmaniasis, a protozoan infection, and lymphogranuloma inguinale, a venereal disease caused by a filtrable virus.

Antimony is not widely used in the United States but is used a great deal in tropical countries. Antimony compounds are highly toxic. The toxic symptoms are similar to those of arsenic.

Preparations.—

Antimony Sodium Thioglycollate, U. S. P. Dose: Intravenously or intramuscularly, 0.05-0.1 Gm.

Antimony Thioglycollamide, N. N. R. Dose: Intravenously or intramuscularly, 0.08 Gm.

Fuadin, N. F. (Stibophen). Dose: Intramuscularly (rarely intravenously) in increasing doses (from 1.5 cc. up to 5 cc.) of 6.3 per cent solution.

Ethylstibamine, N. N. R. (Neostibosan). Adults may receive 0.2 Gm. as the initial dose and up to 0.3 Gm. for subsequent doses. The drug is given intramuscularly or intravenously in 25 and 5 per cent solutions. It is important to give it slowly.

LEPROSY**Chaulmoogra Oil**

Chaulmoogra oil is obtained from the seed of a tree native to the East Indies. It is an old remedy used in the treatment of leprosy. The isolation of the ethyl ester lead to great hopes for the drug. The results of its use have been disappointing, however, and those with much experience with leprosy question the value of the oil and its derivatives. The Council on Pharmacy and Chemistry is of the opinion that present evidence does not support the claims for the use of either the oil or the derivatives in the treatment of leprosy.*

The cures obtained, it is thought, are due to hygienic and dietetic regime, as in tuberculosis.

Preparations.—

Chaulmoogra Oil, N. F. Dose: 1 cc. (15 minims) in capsules, increasing the dose as tolerated. It is usually given by mouth.

Ethyl Chaulmoograte, N. F. Dose, 2 cc. orally or intramuscularly. This is a synthetic derivative of the oil and is less irritating. It may be given orally or intramuscularly.

Sulfones

Three members of the sulfone group of drugs (namely, *Promin*, *Diasone*, and *Promizole*) have been used in the treatment of leprosy at the National Leprosarium in Louisiana with more effective results than have hitherto been obtained.† The parent compound from which these drugs are derived is Diaminodiphenylsulfone. *Promin* is p,p'.

*N. N. R., 1947, p. 114.

†Faget, G. H., and Erickson, Paul T.: *Chemotherapy of Leprosy*, J. A. M. A., 452, (Feb. 14), 1948.

diaminodiphenylsulfone-N,N'-didextrose sulfonate. Diasone is disodium formaldehyde sulfoxylate diaminodiphenylsulfone. Promizole is 4,2'-diaminophenyl-5'-thiazolylsulfone.

Promin is given intravenously because oral administration is said to prove too toxic. Diasone and Promizole have the advantage of being tolerated when given orally.

None of the sulfones produce crystalluria, although both Promin and Diasone may produce a slow destruction of erythrocytes, leukopenia, and allergic dermatitis. Discontinuance of treatment for a week at a time is recommended for patients receiving Promin.

This seems to diminish toxic reactions materially.

The sulfone drugs seem to act slowly and improvement is not seen for a matter of several months. Both early and advanced leprosy is checked and improves under treatment in spite of the fact that recurrences do occur in certain patients.

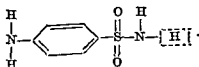
The initial dose of Promin that is recommended is 1 Gm. daily increased up to 5 Gm. daily. Diasone is given in doses of 0.3 Gm. daily and gradually increased if toxic symptoms do not appear. Promizole is administered by mouth in doses of 0.5-1 Gm. three times a day and later increased if well tolerated.

Each of these sulfones is readily excreted by the kidney and careful distribution of dosage is needed to maintain satisfactory blood levels.

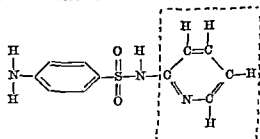
The ultimate status of these drugs in the treatment can be obtained only after further use over a period of years. They at present are not official.

THE SULFONAMIDES

Chemistry.—All of the sulfonamides used therapeutically contain the amino-benzene-sulfonamido group ($\text{H}_2\text{N}-$ — $\text{SO}_2\text{NH}-$) which gives them their common characteristics. To this group is attached hydrogen or other groups which give each sulfonamide its different characteristics as illustrated below:



Sulfanilamide
Shows H attached to amino-benzene-sulfonamido group



Sulfapyridine
Shows pyridine ring attached to amino-benzene-sulfonamido group

Action of Sulfonamides.—The exact way in which the sulfonamides act is not known. It is believed that they interfere with the metabolism of susceptible bacteria, thus inhibiting the bacteria and producing a bacteriostasis so that phagocytes can destroy the bacteria. The concentrations attained by systemic administrations are such that bacteriostasis is produced, but when the concentration is great enough, as in local administration, the action is bactericidal.

One theory concerning their action is that these drugs deprive bacteria of para-amino-benzoic acid, and that this is essential for the growth of susceptible organisms. Thus para-amino-benzoic acid inhibits the action of the sulfonamides.

A more recent theory of the mode of action of the sulfonamides has been suggested. This explains their action on the basis of their chemical similarity to certain coenzyme molecules, which allows the sulfonamides to combine with specific proteins of the respiratory enzymes of cells. Exactly how the sulfonamides act against the cellular respiratory enzyme systems is not yet known.

Absorption.—Sulfanilamide, sulfathiazole, sulfadiazine, and sulfamerazine are absorbed rapidly from the intestines. Sulfapyridine is absorbed irregularly and often poorly from the intestines which is one reason the other drugs are often chosen in preference to it. Sulfaguanidine and succinylsulfathiazole (sulfasuxidine) are absorbed poorly from the intestines and so are used for infections within the intestines. Sulfapyrazine is absorbed rather slowly.

Excretion.—These drugs are excreted chiefly by the kidneys. Sulfanilamide is excreted rapidly, sulfathiazole moderately rapidly, and sulfapyridine, sulfadiazine, sulfamerazine, and sulfapyrazine are excreted slowly. Formation of urinary crystals with blocking of the tubules and pelvis is one of the toxic reactions of these drugs and so it is important to know with which of these drugs this complication is likely to occur. Sulfanilamide causes crystalluria rarely, sulfathiazole and sulfadiazine frequently, and sulfapyridine very frequently. Sulfamerazine is thought to cause crystals as frequently as, or a little more frequently than, sulfadiazine. Anuria, oliguria, hematuria, and presence of a sediment are symptoms of kidney damage and should be watched for by the nurse.

To offset crystal formation in the urine, it is recommended that the urinary output be from 1000 to 1500 cc. per day so that there will be sufficient fluid to dissolve the drug. The output is more important to watch than the intake because of the different amounts of water which may be excreted through the skin under varying conditions, such as in hot and cold climates. Alkalinization of the

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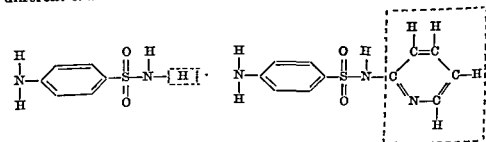
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Sulfapyridine
Shows $[pyridine\ ring]$ attached to amino-benzene-sulfonamido group

Parenteral injections are indicated only when mouth administration is not satisfactory. Oral administration may not be advisable in severe infections, when adequate blood concentrations are needed quickly, in patients who are vomiting, or when the rate of conjugation is too great. The sulfonamide sodium salts are more soluble than other sulfonamides and are given when the parenteral route is necessary. Intravenous injection of 5 per cent solutions of the sodium salts in distilled water is the preferred parenteral method. These solutions are highly alkaline and may cause sloughing if the solution gets outside the vein. Frequent injections may cause thrombosis of the veins. For subcutaneous injection, solutions of the sulfonamide sodium salts in concentrations from 0.3 to 0.7 per cent may be given in isotonic saline.

Dosage.—The dosage of the different sulfonamides varies, depending upon the absorption, excretion, the severity of the infection, and on certain other conditions. The dosage is usually based on body weight.

Blood concentrations of the sulfonamides are done at frequent intervals so that dosage may be decreased if the amount in the blood becomes too great.

Local Administration.—Crystalline sulfonamide powders are used locally in a number of conditions. When administered topically, the drug reaches a high concentration locally but the blood levels can be kept within a safe range. The drug should be sterile and is supplied in ampules or envelopes. Necrotic tissue and pus inhibit the sulfonamides and therefore the wound should be thoroughly cleansed before application of the drug. Local anesthetics such as procaine (novocain) inhibit the sulfonamides because they are esters of para-amino-benzoic acid and break down into it when injected into the tissues. It is suggested that local anesthetics which are not derived from para-amino-benzoic acid should be used if local anesthesia is necessary.

Crystalline sulfanilamide is highly effective locally in hemolytic streptococcic infections. Crystalline sulfathiazole is the drug of choice for staphylococcic infections. Crystalline sulfathiazole tends to cake and thus acts as a foreign body.

The drug should be distributed evenly over the wound, approximately 0.1 Gm. being used per square inch, but not over 10 Gm. per person for a twenty-four-hour period.

Choice of Drug.—The choice of the sulfonamide to be used depends on the type of organism causing the infection, the clinical efficiency of the drug, and the variety, frequency, and severity of the

urine by giving a drug such as soda bicarbonate by mouth is important because most of the sulfonamides are more soluble in alkaline than in acid urine.

Acetylation.—Acetylation (or conjugation) of the sulfonamides is a process by which a certain percentage of the drug taken into the body is changed into a different form. Acetylation is important to the physician in choosing which drug to use because the acetylated forms are believed to be nontherapeutic but may produce toxic symptoms. Thus a drug with a low percentage of acetylation in the body could be given in smaller doses than a drug with a high percentage of acetylation, other factors being equal. Sulfapyridine is acetylated to a high degree and the acetylated form is less soluble in urine than the free form. Acetylated sulfathiazole is also less soluble than free sulfathiazole.

When the blood is examined to determine the amount of the sulfonamide present, it is the blood level of the "free" sulfonamide (i.e., that which is not acetylated) which is important for therapeutic purposes, for it is the free sulfonamide which is able to work against bacteria.

Distribution in Body Tissues.—Sulfanilamide, sulfapyridine, sulfadiazine, sulfamerazine, and sulfapyrazine are distributed in all the body tissues. Sulfathiazole is distributed in all the body tissues except the cerebrospinal, hence it is not used in the treatment of infections of the nervous system.

Administration.—The sulfonamides are usually administered by mouth. Because many of them are well absorbed from the intestines and well distributed to the body tissues and because mouth administration is the safest and most convenient method, it is the method of choice whenever possible. To be effective the sulfonamides must be given at regular frequent intervals so that the proper blood level of drug is maintained. Those which are excreted quickly must be given at intervals of every four hours and this four-hour schedule must be followed, even if the patient has to be awakened to do so. Those drugs which can be given at eight-hour intervals thus have a distinct advantage. Doses which are vomited must be repeated so that the blood level will not fall below effective levels. Inadequate doses are thought to be one of the reasons that certain strains of organisms are able to become sulfa-resistant or sulfa "fast." Administration is generally continued until the temperature has been normal at least seventy-two hours, then the dosage is gradually decreased.

toxic reactions which may be produced. Evidence of clinical efficacy changes rapidly in this field as new data are published.

Toxicity and Treatment.—Toxicity may occur with any of the sulfonamides and is considered to be an individual idiosyncrasy and is unpredictable. In general, sulfanilamide and sulfapyridine are most toxic, sulfathiazole less toxic than the first two mentioned, and sulfadiazine least toxic. Sulfamerazine is so new that it is difficult to evaluate at present, but it seems to be approximately as toxic as sulfadiazine. Sulfaguanidine and succinylsulfathiazole generally do not cause toxic symptoms because they are so poorly absorbed. When renal function is impaired toxicity is more likely to occur. Toxic symptoms which may occur are:

Cyanosis.—This is frequently seen with sulfanilamide, less often with sulfapyridine, and is negligible with the others. It is not usually considered important enough to stop the drug.

Nausea and Vomiting.—This occurs most often with sulfapyridine. It is not common with sulfadiazine and sulfamerazine. It may be lessened by administering the drug in a suspension of tragacanth or in enteric coated tablets. Usually stopping the drug is not indicated.

Dizziness.—This is not so common with the newer preparations and does not require stopping the drug.

Anemia.—A mild anemia does not require stopping the drug but in the case of acute hemolytic anemia the drug is stopped and a blood transfusion may be indicated. Hemoglobin estimations should be done frequently to check a suddenly developing acute anemia.

Jaundice.—This may be due to the development of an acute anemia or to hepatitis. In either case the drug is stopped and if due to hepatitis, a high carbohydrate, low-fat diet is indicated. The nurse should note whether jaundice of the sclera is present, for the jaundice may be noted in the sclera before it can be noticed in the skin.

Acidosis.—This occurs with sulfanilamide and sulfathiazole but not with the other sulfonamides under discussion. To offset this effect, soda bicarbonate is administered. When soda is administered with the other drugs, it is given to render the urine more alkaline and so help prevent the formation of crystals in the urine.

Leucopenia, Granulocytopenia.—If the white blood count is decreased below normal, the drug may be stopped and fluids are forced. Drugs may be given to stimulate blood cell formation (cevitamic acid, nucleotide, yellow bone marrow, and liver extract). Frequent white blood counts should be done to determine whether this complication is developing. These should be done more often the longer the drug is given, for most cases of agranulocytosis develop after two or three

TABLE V

SULFONAMIDE OF CHOICE AS RECOMMENDED BY N. N. R., 1947

MICROORGANISMS	FIRST CHOICE	SECOND CHOICE	THIRD CHOICE	REMARKS
Hemolytic Streptococci	Sulfadiazine Sulfamerazine Sulfapyrazine	Sulfanilamide	Sulfapyridine	Sulfathiazole fourth choice
Lancefield Group A				
Alpha-Hemolytic Streptococci (<i>Streptococcus viridans</i>)				
	Evidence not completely clear. In tissue infections (other than subacute bacterial endocarditis) produced by so-called "mouth varieties," sulfanilamide, sulfathiazole, sulfapyridine, and sulfadiazine seem about equally effective			
Enterococcus type of Streptococci	None is effective			
Pneumococcus	Sulfamerazine	Sulfathiazole	Sulfapyridine	
Staphylococcus	Sulfadiazine Sulfadiazine, Sulfathiazole, or sulfa- merazine			
Meningococcus	Sulfadiazine or Sulfa- merazine	Responds well to sulfathiazole, sulfanil- amide, and sulfapyridine, and sulfapyrazine		
Friedländer's bacil- lus	Sulfadiazine	Sulfapyridine	Sulfathiazole	
Gonococcus	Sulfathiazole or sulfa- diazine	Sulfapyridine		
Gonococcus eye infec- tions	Sulfadiazine orally has been recom- mended			
<i>Bacillus dysenteriae</i>	Sulfadiazine	{ Sulfathiazole Sulfaquandine		Succinylsul- fathiazole is valuable
Actinomyces	Sulfadiazine			
Virus of trachoma	{	Respond to sulfonamide therapy, but data as to relative efficiency of various compounds are not clear cut. Most reports deal with sulfa- nilamide, sulfapyridine, sulfathiazole or sulfa- diazine		
Virus of follicular conjunctivitis				
Virus of lympho- granuloma venereum				
Virus of molluscum contagiosum				
<i>Brucella melitensis</i>	{	Respond to sulfonamides but selection of drug of choice is difficult because of inadequate data		
<i>Pasteurella tularensis</i>				
<i>Clostridium perfrin- gens</i> (<i>Clostridium welchii</i>)				
<i>Clostridium septicum</i>				
<i>Hemophilus influ- enzae</i>				
<i>Ducrey's Bacillus</i>	Sulfanilamide			Others are effective

Sulfapyridine is now known to have limited usefulness and is of value principally in dermatitis herpetiformis. The sulfonamides are ineffective in rheumatoid arthritis and may be dangerous in acute phases of rheumatic fever. (N. N. R., 1947, p. 119). Prophylactic use of sulfonamides for the prevention of pneumonia and complications of common colds or influenza is not recommended.

a single dose. About 10 to 20 per cent of the drug in the circulating blood is in the acetylated form in patients with normal renal function. It is readily excreted by the kidneys. The toxic symptoms though serious are not frequent. They usually include central nervous system manifestations such as headache, dizziness, nausea and vomiting, and sometimes toxic psychoses.

Dosage.—One-tenth of a gram per kilogram of body weight for the initial dose, then about $\frac{1}{6}$ of the initial amount given every four hours is recommended for serious infections. The administration is usually by mouth but subcutaneous injections of 1 per cent solutions in isotonic saline may be given.

Sulfapyridine, N. F.

Sulfapyridine was introduced in 1939. It is poorly and irregularly absorbed in comparison with sulfanilamide and is usually conjugated to a higher degree than sulfanilamide. Because of irregularities of absorption and acetylation, determination of the concentration of sulfapyridine in the blood is very important. The excretion is slower than with sulfanilamide and may take four to five days. Sulfapyridine does not produce toxic reactions as frequently as sulfanilamide, but they may be very severe. Nausea and vomiting are more severe than with sulfanilamide; toxic symptoms may cease, however, as treatment is continued. Since acetylsulfapyridine crystals occur frequently in the urine, it is important to keep the output up to at least 1000 cc. per day.

Dosage.—Examples of dosages recommended are: in lobar pneumonia 4 Gm. as an initial dose, then 1 Gm. every four hours till the temperature is normal for 72 hours. In gonorrhea 3 Gm. may be given the first day, and 2 Gm. for nine successive days.

Sulfathiazole, U. S. P.

Sulfathiazole was introduced in 1940. It is rapidly absorbed from the intestinal tract, maximum concentrations in the blood being reached in three to six hours after administration of a single dose. It does not pass into the spinal fluid. The degree of conjugation is usually slightly greater than with sulfanilamide but less than with sulfapyridine. It is so rapidly excreted that it is sometimes difficult to maintain adequate blood concentrations; excretion is complete twenty-four hours after a single dose. Rashes and fever occur more frequently than with other commonly used sulfonamides. Kidney damage may be due to acetylsulfathiazole crystals, but in some patients it seems to be due to a direct toxic effect on the renal

weeks of treatment with the sulfonamides. A severe sore throat may be the first symptom of this toxic reaction.

Drug Fever.—This complication may necessitate stopping the drug.

Rash.—The rash may be mild in which case the drug need not be stopped, but if it is acute the drug must be discontinued. Patients taking sulfonamides should avoid direct sunlight for dermatitis may develop on exposed areas of the skin surface.

Nervous System Symptoms.—Psychoses may occur, and usually it is advisable to stop the drug. Sulfanilamide produces muscular incoordination and so ambulatory patients should not be allowed to perform hazardous work requiring fine coordination such as driving automobiles or piloting airplanes. Experiments on healthy young men who were given sulfadiazine showed that it does not appreciably alter coordination, hence it may be prescribed for ambulatory patients.

Anuria, Oliguria, and Hematuria.—The reasons for these symptoms and the prevention of them were discussed under excretion. If these symptoms occur, the drug should be discontinued.

Other Complications.—Other complications occasionally occur but the most important have been discussed.

General Treatment of Toxic Symptoms.—The general treatment of any toxic symptom includes stopping the drug and forcing fluids. Because of the many serious toxic reactions which may occur, no one should take any of the sulfonamides unless under the direct supervision of a physician.

Prontosil and Neoprontosil

Prontosil was the first of all sulfonamides to be discovered. It was patented in Germany in 1932. In 1933 the first report of the giving of the drug to a human being was recorded. Prontosil is too insoluble to be given by parenteral injection. In 1935 neoprontosil (prontosil -S or prontosil-soluble) was described. Prontosil may be given only by mouth. Neoprontosil is given orally, subcutaneously, or intramuscularly.

It was later shown that prontosil and neoprontosil act in the body by releasing sulfanilamide. Since this discovery, attention has been focussed on sulfanilamide and sulfanilamide derivatives, and these have almost entirely replaced the prontosils in therapeutic usage.

Sulfanilamide, U. S. P.

Sulfanilamide was the first of the commonly used sulfonamides and was introduced in 1937. It is readily absorbed from the intestinal tract, absorption being practically complete in four hours after

in doses of 0.05 Gm. per kilogram of body weight every eight hours for five days preoperatively. After surgery it is started as soon as the patient can take it by mouth and is continued for seven days in the same dosage as it was given preoperatively.

Succinylsulfathiazole (Sulfasuxidine), U. S. P.

Succinylsulfathiazole is poorly absorbed from the intestinal tract and seems to be less toxic than sulfaguanidine. It is especially valuable in treating infections by gram-negative organisms.

It is used in bacillary dysentery both in treating the disease and in treating carriers. It is also helpful in preventing infections after intestinal surgery. For this latter use the initial dose preoperatively is 0.25 Gm. per kilogram of body weight, followed by 0.25 Gm. per kilogram daily in six equal doses every four hours. Postoperatively the same dose per kilogram of body weight is given daily for one or two weeks.

Sulfamerazine, U. S. P.

Sulfamerazine was accepted by the Council on Pharmacy and Chemistry of the American Medical Association in 1944.

It is quickly absorbed from the intestinal tract and so adequate blood levels can be attained quickly by mouth administration without the use of sodium salts intravenously. Since it is rather slowly excreted by the kidneys, it can be given at eight-hour intervals. It appears to be approximately as effective and as toxic as sulfadiazine. The dosage is 4 Gm. for the initial dose, followed by 1 Gm. every eight hours.

Sulfapyrazine, N. N. R.

Sulfapyrazine is absorbed and excreted rather slowly; hence once the desired blood level is attained the concentration remains fairly constant with a dosage of 1 Gm. every four to six hours, if needed.

Intravenous administration is followed by penetration of the cerebrospinal fluid to the extent of one-half to two-thirds of the concentration found in the blood. It has a low degree of conjugation and appears to have a low level of toxicity in experimental animals.

Symptoms of poisoning when they do occur are similar to those of the other sulfonamides.

Sulfapyrazine is thought to be as effective as Sulfadiazine in the treatment of infections due to *Bacillus coli*, hemolytic streptococci, and pneumococci. It is also effective against *Shigella paradysenteriae* and meningococci.

epithelium. Injection of the sclera and conjunctiva has been reported; this has not been noted with sulfanilamide or sulfapyridine.

Dosage.—An example of a dosage recommended in N. N. R. is: For a diffuse staphylococcic cellulitis 4 Gm. as the initial dose, then 1.5 Gm. every four hours as long as the infection keeps spreading, then 1 Gm. every four hours as indicated.

Sulfadiazine, U. S. P.

Sulfadiazine was introduced in 1941. It is absorbed more slowly and less completely than sulfanilamide and sulfathiazole. It is acetylated to a lesser degree than sulfanilamide, sulfapyridine, or sulfathiazole. It is readily excreted from the kidneys in both the free and acetylated forms. Excretion is usually complete in forty-eight hours after a single dose. It causes fewer toxic reactions than sulfanilamide, sulfapyridine, or sulfathiazole. Acidosis does not occur. Owing to the deleterious effect of sulfanilamide on motor coordination and psychomotor status of the average young adult, the Surgeon Generals of the Army and Navy have ordered sulfadiazine to be used in place of sulfanilamide, since it is as effective therapeutically and has little or no effect on motor coordination.¹

An example of a recommended dosage is: In adult suffering from severe hemolytic streptococcic infections, an initial dose of 0.1 Gm. per kilogram of body weight, then 1 Gm. or 1.5 Gm. every four hours till the temperature has been normal five to seven days.

Sulfaguanidine, U. S. P.

Sulfaguanidine though soluble in the intestinal contents is poorly absorbed from the intestines and so exerts its bacteriostatic and bactericidal action locally in the intestine. Under proper administration the blood concentrations usually do not go above 5 mg. per 100 cc. of blood. It is less toxic than the sulfonamides which are well absorbed from the intestines. Only rarely do patients get toxic symptoms. If toxic reactions do occur, enemas are indicated in addition to the usual forcing of fluids.

Dosage.—In bacillary dysentery 0.05 Gm. per kilogram of body weight is given every four hours till the number of stools is five or less daily, then the dosage can be decreased. If no improvement occurs in seven days, it is likely that the drug will not be effective. The drug usually is not administered for more than fourteen days.

It has also proved useful in preventing infections when surgery is performed on the intestine. For the latter use it is administered

¹Queries and Minor Notes, J. A. M. A. 122: 70 (May 1), 1943.

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Preparations.—

The sulfonamides may be dispensed as tablets or in powder form. The powder may be in bulk form or may be sterile and is then dispensed in ampules or envelopes.

Sulfanilamide (Sulfanilamidum), U. S. P. Dose: 2 Gm. (30 gr.).

Sulfapyridine (Sulfapyridinum), N. F. Dose: 2 Gm. (30 gr.).

Sterile Sulfapyridine Sodium (Sulfapyridinum Sodicum Sterile), N. F. Dose: 2 Gm. (30 gr.).

Sulfathiazole (Sulfathiazolum), U. S. P. Dose: 2 Gm. (30 gr.).

Sulfathiazole Sodium (Sulfathiazolum Sodicum), U. S. P. Dose: 2 Gm. (30 gr.).

Sterile Sulfathiazole Sodium (Sulfathiazolum Sodicum Sterile), U. S. P. Dose: Intravenous, 2 Gm. (30 gr.).

Sulfadiazine (Sulfadiazinum), U. S. P. Dose: 2 Gm. (30 gr.).

Sterile Sulfadiazine Sodium (Sulfadiazinum Sodicum Sterile), U. S. P. Dose: Intravenous, 2 Gm. (30 gr.).

Sulfaguanidine (Sulfaguanidinum), U. S. P. Dose: 2 Gm. (30 gr.).

Succinylsulfathiazole (Succinylsulfathiazolum), U. S. P. (Sulfasuxidine). Dose: 2 Gm. (30 gr.).

Sulfamerazine, U. S. P. Dose: 2 Gm. (30 gr.).

Sulfamerazine Sodium, U. S. P. Dose: 2 Gm. (30 gr.).

Sulfapyrazine, N. N. R. Dose: 2 to 4 Gm. (30-60 gr.) followed by 1 Gm. every 4 to 6 hours.

ANTIBIOTICS**Penicillin, N. N. R.**

Penicillin is a solid antibacterial agent secreted by *Penicillium notatum*, the common green bread or cheese mold. Agents such as penicillin are called antibiotics or antimicrobial agents of biologic origin. The story of its discovery and development is discussed in Chapter XXIII. The exact chemistry of penicillin has not yet been determined, but it is known to be an acid. The various forms of penicillin so far isolated have been designated as F, G, K, and X. Amorphous mixtures have been widely employed in the form of their sodium or calcium salt. Crystalline preparations have also been developed. These are of greater purity and stability and may contain more than one kind of penicillin or they may contain chiefly penicillin G in the form of its sodium or potassium salt.

Action.—Penicillin is bacteriostatic in a large variety of infections. Concentrations strong enough to be bacteriostatic are not

NURSING CARE

The most important points in the nursing care of a patient receiving sulfonamides are as follows:

1. Doses must be given on time. No dose should be omitted and so patients on a four-hour schedule must be awakened at night. Vomited doses should be repeated.

2. Usually bed rest is ordered for patients receiving sulfonamides. Ambulatory patients should not be allowed to go out in the sun. They should follow the doctor's advice about driving cars and staying away from work requiring careful judgment or involving danger.

3. If a sputum specimen is ordered, it should be obtained before starting the sulfonamides.

4. The urine should always be measured and the output should not be below 1000 cc. per day. Some physicians ask that the urine output be kept above 1500-2000 cc. per day. Generally, fluids by mouth are forced to 2500-3000 cc. to insure adequate output.

5. If patients have difficulty in taking tablets, they should be crushed and dissolved in water. For children, crushed tablets can be mixed with syrup or dissolved in water and given with a spoon or medicine dropper. Pulverizing the tablets and giving the powder in milk, fruit juice, or applesauce may make the preparation easier to take for patients who are nauseated.

6. The nurse should observe all patients carefully for toxic symptoms and report them promptly. Nausea, vomiting, fever, sore throat, hematuria, anuria, gross crystals in the urine, jaundice, conjunctivitis, and rash are symptoms the nurse should especially watch for.

7. All laboratory tests such as blood tests and urinalysis should be done at the time designated by the doctor so that toxic symptoms will be noted early.

8. The nurse should endeavor to impress upon patients the importance of medical supervision so that patients will not regard sulfonamide therapy as a simple type of medication. If some sulfonamide tablets are left over after the termination of an illness, patients should be taught that they are potentially dangerous drugs which should not be used for any respiratory infection (or other infection) which may occur later. Inadequate dosage is as dangerous as overdosage because organisms can become sulfonamide resistant and because in diseases such as gonorrhea symptoms may be masked temporarily.

9. If conjunctivitis occurs, the eyes should be protected from light because photophobia is usually present.

may cause venous irritation, (2) the drug disappears quickly from the blood (approximately 90 per cent disappears from blood in thirty minutes), and (3) it is time-consuming for the medical staff who must give the frequent injections.

b. Continuous Drip.—Twenty-five to fifty units per cc. of penicillin may be dissolved in isotonic sodium chloride or 5 per cent dextrose. This method is advantageous in that the blood level of penicillin can be more evenly controlled than by intermittent injections, it seems to require a smaller dosage, and it requires less time from the medical staff. A simple arm splint is applied and the needle has been left in as long as eight days, though the site must be changed if venous irritation occurs.

2. Intermittent Intramuscular Injection: Five thousand units may be dissolved in 1 cc. of isotonic sodium chloride. Penicillin is usually given every three hours intramuscularly. If an icecap is placed on the buttock half an hour before the injection, it lessens pain because cold acts as an anesthetic, and prolongs absorption because cold slows the circulation. Though the initial blood level is not as high as by the intravenous method, the blood level maintains a higher concentration for a longer time and so this method is favored by many doctors. Another advantage is that the technique of administration is simpler and can be performed by nurses, which relieves the medical personnel. Numerous intramuscular injections are better tolerated by most patients than the multiple intravenous injections.

Experiments with administration by continuous intramuscular drip are being made with promising results, and this method may become popular.

3. Subcutaneously: Penicillin is slowly absorbed after subcutaneous injection. The main advantage of this method is that the frequent needling is avoided and the extremities do not need to be immobilized. However, the absorption is said to be erratic and may be painful, and so this method has not gained wide use.

4. Intrathecal Administration: For intraspinal injection 1000 units per cc. of isotonic sodium chloride in total doses of 10,000 units once or twice a day may be injected. When the meninges are normal, little penicillin is found in the spinal fluid after intramuscular or intravenous injection. There is evidence that when the meninges are inflamed some penicillin does get from the blood stream into the cerebrospinal fluid. However, in meningitis it is considered necessary to inject the penicillin intraspinally for good

injurious to body cells and its action is not affected by pus, blood, serum, or the number of bacteria present.

Measurement.—Penicillin was originally measured in terms of Oxford units. This unit was introduced by the Oxford group of scientists who have done much research on the drug. It was defined as that amount of penicillin which, when dissolved in 50 ml. of meat extract broth, just inhibits completely the growth of the test strain of *Staphylococcus aureus*. A unit as defined in the U. S. P. is the penicillin activity contained in 0.6 microgram of the Food and Drug Administration master standard. The term master standard means a specific lot of penicillin G which serves as the standard of comparison in determining potency. This unit is approximately equivalent to the original Oxford unit. Potency is assayed by bacteriologic testing against a strain of *Staphylococcus aureus* or other suitable organisms.

Administration.—Penicillin is supplied as a dry powder in ampules or rubber-capped vaccine vials, each containing 100,000 units. It is very soluble and may be dissolved in sterile distilled water, isotonic solutions of sodium chloride, or in 5 per cent dextrose. Exposure to air, heat, alcohol, or acid causes penicillin to lose its potency. The solution should be made up fresh every day (or not longer than two or three days ahead) and kept in the refrigerator in rubber-capped containers. The drug must be handled aseptically, for certain bacteria (for example *E. coli*) destroy it. Solutions should not be heated. Syringes and needles used for penicillin should be sterilized by boiling or autoclaving and not by the use of alcohol, unless the alcohol can be removed by drying or evaporation.

Penicillin when administered by mouth must be protected from the acid of the stomach which destroys it. Because it is excreted very quickly, it is usually injected every three hours. These doses must be given on time and, if necessary, patients must be awakened to receive the drug. If it is given by continuous drip, the solution should be regulated so that the flow is continuous. It cannot be given rectally because certain bacteria (*E. coli* for example) secrete an enzyme which inactivates it.

It is given in the following ways:

1. **Intravenously:**

a. **Intermittently.**—The powder may be dissolved in sterile isotonic sodium chloride in concentrations of 1000 to 5000 units per cc. for direct injection with a syringe. The doses are usually given every three hours because it is very rapidly excreted by the kidneys. The disadvantages of this method are: (1) the frequent injections

10. Inhalation: An aerosol of penicillin can be made and administered with a suitable nebulizer. It has been found useful for inhalation for patients with pulmonary infections due to penicillin-sensitive organisms. The solution used usually contains 25,000-50,000 units per cubic centimeter. This type of aerosol has been found of value in the treatment of pneumonia if the patient is not seriously ill. It is a way of avoiding repeated injections of penicillin.

EXCRETION.—Penicillin is rapidly excreted in large amounts in the urine. It is found in higher concentrations in the bile than in the blood and so the liver probably excretes some penicillin.

TOXIC REACTIONS.—There are practically no toxic reactions to penicillin. Some of the earlier batches of penicillin contained pyrogens which caused febrile reactions. As more experience is gained in its preparation, the penicillin on the market is becoming more pure and with these purer preparations, febrile reactions are being noted less often.

The following reactions are of importance:

1. Local irritation. Venous irritation may develop from either the continuous or intermittent intravenous injections. Local irritation may occur at other sites also. These must be watched for but usually are not serious.

2. Urticaria or irritative dermatitis. This occurs infrequently but should be watched for carefully, because the patient is probably hypersensitive and if the drug is continued, in some cases the dermatitis may become severe. Antihistaminic drugs have proved to be effective in relieving skin symptoms.

3. A few patients develop diarrhea which usually can be controlled by paregoric.

4. Patients who receive penicillin for syphilis may experience Herxheimer reactions. This is not an indication for stopping treatment.

ORGANISMS AGAINST WHICH PENICILLIN IS EFFECTIVE*

Staphylococcus aureus
Hemolytic streptococci
Anaerobic streptococci
Diplococcus pneumoniae
Neisseria gonorrhoeae
Neisseria intracellularis meningitidis
Bacillus anthracis
Organisms of gas gangrene
Clostridium botulinum
Clostridium tetani

*Modified from Table I. From Herrell, W. E., Nichols, D. R., Hellman, D. H.: Penicillin, J. A. M. A. 125: 1004 (August 12), 1944.

results. It is slowly absorbed by the blood and excreted by the kidneys. It can be detected in the cerebrospinal fluid more than twenty-four hours after injection.

5 **Intrapleurally:** In patients with empyema 30,000 to 40,000 units of penicillin may be injected after the pus is aspirated.

6. **Intra-articularly:** Penicillin is injected into the joints in suppurative arthritis. The drug does get to the joints following intramuscular or intravenous injection but if it is thought desirable to supplement amounts given by other means, the drug may be injected after aspiration of the joints.

7. **Eye:** Penicillin enters the eyeball after intramuscular or intravenous injections. It also enters the eyeball after application of a cup bath or by iontophoresis. It can also be administered by subconjunctival injection. Ointments containing penicillin are used for local conditions such as irritation of the lids.

8. **Topical Application:** Penicillin is applied locally to infected wounds and burns. For local application 250 units per cc. (or 500 units per cc. in severe cases) in isotonic sodium chloride solution may be used.

Penicillin ointment is also used locally. Dry powdered penicillin has been used for local conditions. The sodium salt should not be used in the powder form, for it is irritating. Some experiments in which penicillin and sulfanilamide powders have been mixed suggest that these two drugs may have a synergistic action.

Penicillin irrigations are not advised because by this method the drug is not in contact with the tissue for a long enough time to be effective, and it is too precious to waste.

9. **Orally:** Penicillin administered by mouth is effective if the drug is protected from the acid of the stomach. When given as a suspension in a digestible oil or accompanied by a mild antacid, the amounts absorbed from the intestine are sufficient to be therapeutically effective. Which vehicle will prove to be most satisfactory is not yet known. The dose by mouth must be four or five times the amount given by injection to be effective. It is preferable to give it between meals. Presumably, crude or impure penicillin could be given by mouth; therefore oral penicillin would be less expensive to prepare and this would probably offset the cost of the greater amounts needed.¹

The calcium salt of penicillin is used in the form of troches for topical effects against Vincent's stomatitis and certain other mouth infections.

¹Editorial: Oral Penicillin, J. A. M. A. 127: 1128 (April 28), 1945.

clinical symptoms are the best criteria in judging the adequacy of dosage for a particular case.

Preparations.—

Penicillin Calcium, U. S. P. Dose: Orally, on a fasting stomach, 300,000 units; intramuscularly, 300,000 units.

Penicillin Sodium, U. S. P. Dose: Orally, on a fasting stomach, 300,000 units; intramuscularly, 300,000 units.

Penicillin Dental Cones, U. S. P. Composed of penicillin calcium and suitable harmless diluents with or without sulfanilamide or sulfathiazole or both. Dose: 1 cone.

Penicillin Injection in Oil and Wax, U. S. P. A sterile suspension of penicillin calcium in a menstruum of peanut oil or sesame oil in which white wax is dispersed. Dose: Intramuscularly, 300,000 units.

Penicillin Ointment, U. S. P. Should be preserved in collapsible tubes at a temperature not above 15°.

Penicillin Tablets, U. S. P. Contain penicillin calcium or penicillin sodium buffered with calcium carbonate, anhydrous sodium citrate, aluminum hydroxide, or other buffers approved by the Federal Food and Drug Administration. Each tablet contains 20,000 to 25,000 units. Dose on a fasting stomach, 300,000 units.

Penicillin Troches, U. S. P. Composed of penicillin calcium or penicillin sodium, or both, and one or more suitable and harmless diluents, binders, etc., as approved by the Federal Food and Drug Administration. Troches are made to contain 500, 1,000, and 20,000 units. Dose: 1 troche.

Streptomycin, N. N. R.

Streptomycin is an antibiotic substance obtained from certain strains of *Streptomyces griseus*. It is able to inhibit and, under certain conditions, to destroy certain gram negative bacteria. It is marketed in the form of hydrochloride and sulfate salts in vials containing the equivalent of 1 Gm. of streptomycin base.

Streptomycin and its salts are reasonably stable, particularly when stored in the form of the dry powder. Solutions of streptomycin should be made fresh for parenteral injection and, when stored, kept in refrigeration.

Administration.—Streptomycin is not well absorbed when given by mouth. For satisfactory systemic effects it should be given by intramuscular or subcutaneous injection except in the case of meningeal infections, when the intrathecal method must be employed.

Clostridium perfringens (welchii)

Corynebacterium diphtheriae (supplemented by antitoxin)

Treponema pallidum (results are very promising but whether they will be lasting is difficult to judge at present)

Actinomyces bovis

Bacteria causing endocarditis (if they are susceptible organisms)

Penicillin is not effective against gram-negative bacilli such as the organisms of undulant fever, tularemia, influenza, the colon-typhoid-dysentery group, and Friedländer's bacillus, or against rickettsiae, or viruses, or the tubercle bacillus.

Penicillin-Resistant Strains.—Strains of *Staphylococcus aureus*, Pneumococci, and hemolytic streptococci can be made penicillin resistant by exposing them to penicillin over long periods of time. Strains resistant to penicillin may develop during penicillin therapy in man. Fortunately this is rare, and when it develops there is proportional loss of virulence. Organisms such as *Staphylococcus aureus*, which become penicillin-fast, can be treated with the sulfonamides.

Dosage.—The dosage of penicillin varies with the nature of the infection and the causative organisms. It is particularly effective in infections due to gram positive bacteria—staphylococci, streptococci, pneumococci and clostridial organisms. It is also effective against gram negative organisms such as meningococci and gonococci.

In serious penicillin-susceptible infections, with or without bacteremia, the average daily dose is 120,000 to 240,000 units. In acute gonorrhea doses of 30,000 units every three hours may be given to patients who are hospitalized. As an aerosol, 25,000 to 50,000 units per cubic centimeter may be nebulized and inhaled every three or four hours. In chronically infected injuries, proper surgical intervention may be combined with 20,000 to 40,000 units of penicillin every three hours.

Although penicillin is considered an adjunct in the treatment of syphilis rather than a substitute for arsenic and bismuth preparations until the curative value of penicillin is determined, large doses are believed to be effective. In seronegative primary syphilis 60,000 units should be given every two or three hours until 3,600,000 units are given. In seropositive primary and early secondary syphilis 60,000 unit doses are given until a total of 5,400,000 units have been administered.*

Inadequate dosage may create resistance in organisms that would otherwise be susceptible. Negative cultures and disappearance of

*N. N. R., 1947. p. 147.

gram-positive organisms and include Pneumococci, Streptococci, and Staphylococci. Gram-negative bacteria inhibit its action.

Administration.—Tyrothricin must be used locally. It is destructive to red blood cells and so must not be given where it can come in contact with blood. It is reported to be of value in treatment of superficial indolent ulcers, mastoiditis, empyema, and some wound infections. It may be used with caution in body cavities. It is ineffective when given by mouth.

Dosage.—Tyrothricin is diluted with isotonic salt solution in sterile distilled water to make a solution of 500-1000 micrograms of drug per cubic centimeter and applied locally as an aqueous suspension or in the form of a cream.

Preparations.—

Tyrothricin Concentrate (Sharp & Dohme, Inc.).

1 cc. ampul of a solution of tyrothricin, 25 mg. per cc. (accompanied by a diluent).

20 cc. ampul of a solution of tyrothricin, 25 mg. per cc. (not accompanied by a diluent).

Solution Tyrothricin (Parke, Davis). 10 cc. vials; each cubic centimeter contains 20 mg. Tyrothricin in 92 per cent alcohol.

Bacitracin

Bacitracin is an antibiotic preparation obtained from the *Bacillus subtilis* group of organisms. It has been used for local applications in the treatment of ulcers, boils, and furuncles. It inhibits growth of staphylococci and nonhemolytic streptococci. It is not inhibited by plasma, blood, or dead tissue. It seems to be particularly effective when the infection is due to a mixture of organisms

Test Questions on Chemotherapeutic Agents

QUININE, ATABRINE, AND PLASMOCHIN

1. What is the natural source of quinine?
2. Is atabrine or quinine better for the treatment of malaria during pregnancy? Why?
3. What is the action of quinine when it is used to treat varicose veins? What preparation of quinine is used for this purpose? How is it administered? What is one danger in its administration?
4. Name four important symptoms of mild quinine poisoning:

a.	c.
b.	d.
5. Is the yellow color which occurs in patients taking atabrine due to jaundice? Is it an indication for stopping the drug? Explain why.

Uses.—Streptomycin has given evidence of usefulness in the treatment of a number of gram negative bacillary infections including tularemia, *Hemophilus influenzae*, meningitis, and pneumonia, urinary infections due to *Escherichia coli*, *Bacillus proteus*, *Pseudomonas aeruginosa*, and *Aerobacter aerogenes*, as well as plague, meningitis due to gram negative bacilli, Shigella dysentery, and infections due to *Klebsiella pneumoniae*.*

Streptomycin is being investigated as a therapeutic agent in the treatment of tuberculous infections, and although it appears to be useful in the treatment of certain kinds of tuberculosis, the extent of its usefulness is still undetermined.

Dosage.—Dosage of this antibiotic is determined by the sensitivity of the infecting organism. In acute infections 2 or 3 Gm. daily may be given in divided doses three or four hours apart. In chronic or less severe infections dosage of 1 to 2 Gm. daily may be sufficient. Treatment should be continued forty-eight to seventy-two hours beyond the time of disappearance of symptoms. Inadequate dosage predisposes to the development of resistance on the part of the infecting organisms.

Toxicity.—Large doses and prolonged administration may give rise to toxic symptoms of varying severity. The most serious of these symptoms is related to involvement of the vestibular (and sometimes Cochlear) branch of the 8th cranial nerve. This gives rise to dizziness ringing in the ears and some difficulty in locomotion. Involvement of the cochlear branch of the nerve will give rise to loss of hearing. The latter effect is less common but both types of symptoms may necessitate stopping the use of streptomycin. Other toxic symptoms include urticaria, pain about the region of the injection, skin rashes, fever and decreased kidney function.

Tyrothricin, N. N. R.

Tyrothricin was accepted for N. N. R. by the Council on Pharmacy and Chemistry in April, 1944. It is an extract made from *Bacillus brevis*, an organism growing in the soil. Tyrothricin contains at least two substances, gramicidin and tyrocidin. Gramicidin is much more active than tyrocidin. The use of tyrothricin is still in the experimental stage.

Action.—Tyrothricin appears to act by inhibiting enzyme action, retarding growth, and causing lysis of susceptible bacteria. The organisms which show some degree of susceptibility are certain

*Report of the Council on Pharmacy and Chemistry, J. A. M. A. 839, (Nov. 29), 1947.

2. What is the chief reason for sulfadiazine being chosen for Mr. Black?-----

3. Which of these orders will be carried out as a measure of the effectiveness of the drug? -----

4. Which of these orders will be carried out to detect toxicity of the drug?-----

5. Place a check after the reason why codeine was ordered for Mr. Black—
 - a. To assist phagocytosis -----
 - b. To put the patient to sleep and thus relieve dyspnea -----
 - c. To relieve coughing -----
6. What other drug ordered for Mr. Black will assist codeine in producing the desired effect? -----
7. Place a check after the reason why sodium bicarbonate was ordered for the patient—
 - a. To prevent crystalluria -----
 - b. To prevent or relieve nausea and acidosis -----
 - c. To provide an unfavorable medium for the growth of streptococci -----
8. Place a check after the symptoms which you regard as toxic manifestations of sulfadiazine—
 - a. Hematuria -----
 - b. Nausea and vomiting -----
 - c. Vertigo -----
 - d. Anemia -----
 - e. Leucopenia -----
 - f. Cyanosis -----
9. Place a check after the symptoms which would probably necessitate stopping the administration of the drug—
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PENICILLIN AND TYROTHRICIN

1. What precautions should a nurse observe in giving penicillin intramuscularly?
2. What toxic symptoms may occur during penicillin therapy?
3. If a solution of penicillin becomes contaminated, would you use heat to sterilize it?
4. Why must penicillin be handled aseptically when it is such an effective bacteriostatic?
5. If you were working in a drug supply room, how much penicillin solution would you make up ahead of time? What precautions would you observe in keeping the penicillin solution?
6. Against which organisms is tyrothricin effective? How do these organisms stain with Gram's Stain?

6. If the skin becomes yellow when a patient is taking plasmochin, is this an indication for stopping the drug?
Why?
7. Is atabrine or plasmochin better for treating clinical attacks of malaria?
Explain why.
8. How is quinine usually administered in malaria?
9. How could you administer atabrine so that toxic reactions would be avoided?

AGENTS USED TO TREAT SYPHILIS

1. If you were a nurse working in a venereal disease clinic, why would it be especially important for you to encourage patients to return faithfully for treatment?
2. In the following list check those items which you would do in helping with the administering of neosalvarsan:
 - use distilled water to dissolve it.
 - prepare the day's supply and keep it in the refrigerator.
 - prepare a tray for intravenous injection.
 - prepare a tray for intramuscular injection.
 - be prepared to neutralize the solution with sodium hydroxide.
 - have the patient remain for ten or fifteen minutes after the injection.
 - have epinephrine ready in case of emergency.
 - have caffeine sodium benzoate ready in case of emergency.
3. What is meant by a course of neocarsphenamine?
4. Which drug is usually given with an arsenical in the treatment of syphilis?
How is this drug administered?
5. Which arsenical is especially well suited to treat syphilis of the nervous system?
6. Why is the nitritoid crisis so called?
7. If a patient asked you why his doctor is not treating him with the "one-day cure," what would you say?

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7. What is the greatest disadvantage of tyrothricin?
8. What precaution must be observed in administering tyrothricin?
9. In what respect does streptomycin differ from penicillin?

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UNIT XII

CHAPTER XXI

PHARMACOLOGY AS RELATED TO METABOLISM AND NUTRITION

MINERAL SALTS

Mineral salts are used to overcome a deficiency of salts in the body. Those most commonly used are calcium and phosphorus. For the utilization of salts, vitamins are essential.

Calcium

Calcium is necessary to the body for the growth of bone, for the regulation of the activities of nerves, muscles and glands, for the maintenance of cardiac and vascular tone, and for the normal coagulation of blood. The intake of calcium in a balanced diet is sufficient for normal needs of the body, but in diseased conditions associated with a deficiency of calcium, the drug is administered in the form of its soluble salts, usually the chloride and lactate. When the calcium concentration of the blood is below normal, the continued administration of soluble calcium salts, especially calcium lactate, increases the calcium content to some extent but it falls rapidly when the drug is discontinued.

Calcium Requirements.—The average adult needs approximately 0.8 Gm. of calcium daily, but pregnant women or lactating mothers as well as growing children frequently need at least twice this amount.*

Absorption and Excretion.—The absorption of calcium will depend upon how well it is kept in solution in the digestive tube. An acid reaction favors calcium solubility, hence calcium is absorbed mainly in the upper intestinal tract. Absorption is decreased by the presence of alkalies, large amounts of fatty acids with which the calcium forms insoluble soaps, and by the presence of diarrhea. Adequate intake of vitamin D appears to promote calcium absorption. A normal individual excretes calcium both in the feces and in the urine.

*Committee on Food and Nutrition, National Research Council—"Nutrition." May-June, 1941.

Action.—

1. *Local*.—Certain salts of calcium, particularly calcium chloride, are intensely irritating to subcutaneous tissues and are likely to cause painful sloughing when given in that manner. When given intravenously, care must be exercised to prevent the solution from escaping into the surrounding tissues.
2. *Systemic*.—Calcium deficiency affects the peripheral neuromuscular mechanism resulting in twitching and spasms in the muscles involved. Either a deficiency or an excess of calcium alters the function of the heart muscle. The absence or deficiency of calcium causes the potassium salts to be more prominent in their effect, resulting in undue relaxation of the heart and cessation of beating. An excess of calcium produces a prolonged state of contraction known as "calcium rigor."

Calcium is necessary for the normal clotting of blood since it functions in the conversion of prothrombin to thrombin. The administration of calcium, however, for prolonged bleeding time has not been accompanied by significant results. This is probably due to the fact that calcium deficiency is rarely responsible for the condition.

The basic salts of calcium act as antacids to control gastric acidity.

Uses.—

1. Calcium salts are specifics for low calcium tetany.
2. Encouraging results have been reported for the use of calcium as an antispasmodic in cases of abdominal pain, tenesmus, gall bladder and ureteral colic.
3. As antacids.
4. Calcium chloride is sometimes given for its diuretic action.

Preparations.—

Calcium Chloride, U. S. P., occurs as white, translucent crystals, having no odor and a sharp saline taste. It is very deliquescent and should be kept in well-stoppered bottles.

Dose: 1 Gm. (15 gr.).

Calcium Lactate, U. S. P., is a white crystalline powder having no odor and almost no taste.

Dose: 5 Gm. (75 gr.).

Calcium chloride is best administered in dilute solution sweetened with syrup or elixir. It may also be injected intravenously in a 5 per cent solution, but it is irritating to the tissues. Calcium lactate

is less irritating than the chloride and is therefore more suitable for hypodermic use. (Inject slowly.)

Calcium Gluconate, U. S. P., is the normal calcium salt of gluconic acid. It is used to obtain the therapeutic effects of calcium. It has an advantage over calcium chloride in that it is more palatable for oral administration and is nonirritant for parenteral use. The oral dose for adults is 5 grams three times a day while the intravenous or intramuscular dose for adults is 1 gram every day or every second or third day.

One part of calcium gluconate is soluble in 30 parts of cold water or in 5 parts of boiling water. Hence some physicians expect the nurse to routinely dissolve the preparation in hot water before giving it to the patient.

Dibasic Calcium Phosphate, U. S. P., is a valuable source of the calcium ion, although this salt is used chiefly as an antacid. This preparation of course supplies both calcium and phosphorus. It is a relatively insoluble, tasteless white powder which must be given orally.

Dose: 1-5 Gm.

Iodine

Iodine is a nonmetallic element found in seaweed. In therapeutics, it is used in the form of sodium iodide and the compound solution of iodine to prevent the development of simple goiter, especially among school children in those mountainous and inland regions in which goiter is prevalent. Simple goiter is an enlargement of the thyroid gland which is believed to be due to a deficiency of iodine in the drinking water. For the prevention of goiter 2 Gm. (30 grains) may be given twice a year in doses of 0.2 Gm. (3 grains) daily for 10 consecutive school days, or a dose of 0.01 Gm. ($\frac{1}{10}$ grain) may be given once a week throughout the school year. Sodium iodide is also given in the form of *iodized salt*. The iodized salt commonly sold in the United States contains 0.1 Gm. ($1\frac{1}{2}$ grains) of sodium iodide in each kilogram of salt. Ten grams of this salt, the average amount consumed daily by one person, contain 1 mg. of sodium iodide. This amount may prove harmful to some persons since the optimum dose and the amount sufficient to prevent the development of goiter is 0.05 mg.

Sodium iodide is also used in the treatment of exophthalmic goiter to lower the rate of metabolism and to lessen nervous excitability and irritation. These depressant effects as a rule do not last long, but are of great value in preparing an exophthalmic patient for operation.

Iodine when taken internally is converted in the stomach and intestines into iodides, which after absorption act in the same manner as sodium iodide. The Strong Solution of Iodine, U. S. P., or Lugol's solution contains about 5 Gm. of iodine and about 10 Gm. of potassium iodide in 100 cc. of distilled water. Its action and uses are the same as those of sodium iodide. For the prevention of simple goiter, the dose is 0.1 cc. ($1\frac{1}{2}$ minims) three times a day. For the pre-operative treatment of exophthalmic goiter patients, 0.5 cc. (8 minims) may be administered one to three times a day for a week or ten days prior to the operation.

Tincture of iodine has been used as an antidiarrheic. The dose is 10 drops in half a glass of water. Its use for this purpose is said to be effective although on an empiric basis.

VITAMINS

Drugs having an outstanding effect on metabolism are the vitamins and hormones.

The discovery and recognition of the importance of vitamins (*vita*, life + amine) have been quite gradual. In 1720, Kramer wrote (*Medecina Castrensis*) that neither medicine nor surgery could give relief in scurvy. "But if you can get green vegetables, if you can prepare a sufficient quantity of fresh antiscorbutic juices, if you have oranges, lemons, citrons, or their pulp and juice, preserved with whey in cask, so that you can make a lemonade, or rather give to the quantity of 3 or 4 ounces of their juice in whey, you will, without other assistance, cure this dreadful evil" (Sherman and Smith). J. Lind* states that "something contained in the juices of the plant (lemon) cures scurvy." In 1847, G. Budd ascribed the action of antiscorbutic foods "to an essential element, which it is hardly too sanguine to state, will be discovered by organic chemistry or the experiments of physiologists in a not far distant future" (Sherman and Smith). In 1820, Magendie found that protein is a necessary factor in animal diet. Without protein in their food, dogs lose weight, develop xerophthalmia, and die within three to five weeks.

In 1880, Takaki succeeded in reducing enormously the incidence of beriberi in the personnel of warships by means of an improved diet.

In 1881, Lunin reported that young mice do not thrive on a diet composed of the proximate principles of milk, which contained fats, proteins, carbohydrates, and salts. He stated that the presence of *unknown substances* in the food is necessary for life.

*Treatise on Scurvy, ed. 2, London, 1757.

Between 1887 and 1898 Eijkman, of Utrecht, showed that chickens fed on polished rice, as their sole food, developed the essential features of beriberi. In 1905, Pekelharing of the same university, as the result of experiments with mice, expressed the belief that an adequate diet must contain essential substances, still unknown.

In 1896, Gowland Hopkins, speaking of his own experiments, opened up a still wider horizon. He said: "In diseases, such as rickets and scurvy, we have for long years knowledge of a dietetic factor, but though we know to benefit these conditions empirically, the real errors in the diet are still obscure. They are, however, minimal qualitative factors."

In 1901, Widliors* found that yeast in a dilute solution of sugar containing the necessary salts for growth will not grow rapidly unless a material extracted from yeast, or other living matter, is added to the solution. He called the added material *bios*. It is now known that the added substance is a vitamin. The nature of it is not yet known though it is said to be a complex inositol compound.

In 1911 Casimer Funk announced that there is a substance essential to life which is not fat, protein, carbohydrate, or salts. To this substance he gave the name *vitamine*, because he thought it was an amine. Some of them at least, probably all, are not amines. Funk was impressed by the development of beriberi in rice-eating countries, due to eating polished rice. Unpolished rice did not cause it. In the polishing, the germ and the bran may be removed. On adding these again to the polished rice the disease is remedied.

Funk isolated a definite chemical substance, related to the pyrimidines, now called vitamin B, from rice bran and from yeast. When 2 to 8 mg. of this substance were given to pigeons with neuritis, they were cured with astonishing rapidity.

A vitamin is now defined as an essential constituent of the diet, organic in nature, and effective in minute amounts. In the early days of vitamin research they were likened to enzymes, and it was thought that they acted catalytically. Opinion now regards them as akin to hormones. Some call them exogenous hormones, because of similarity in action to the glands of internal secretion. They have been named alphabetically, A, B, C, D, E, F, G, etc., according to the order of their discovery. B has been found to be a complex of vitamins. Study has shown that F belongs to the B₁ complex. They are now named A, B, B₁, B₂, C, D, E, etc. Four or more B's have been recognized, but are not yet accepted as definite entities. The reason for

**La Cellule*, 1901, chap. XVIII.

this difference in nomenclature is that what some have called F and G are closely related to the original B.

Vitamins are divided into two groups:

1. Lipid-soluble vitamins, A, D, E.
2. Water-soluble vitamins, B or B₁, B₂(G), C, and somewhat doubtful B₃, B₄, B₅, and B₆.

Vitamins in general are present in the natural foods, particularly in glandular organs, milk, eggs, butter, green vegetables, and yeast. They are relatively deficient in meats, flour, some oils, and sugar.

Inadequacies of nutrition have too long been thought of in terms of actual deficiency diseases which for the most part are easily detected, and we have failed to recognize the hordes who fall into the class of submarginal deficiency. People who subsist on deficiency diets are usually not sick enough to consult a doctor, but they are far from being well enough to meet effectively the stress and strain of ordinary modern living.

It has become obvious that vitamin deficiency may exist in what is supposedly a normally adequate diet. This is particularly likely to occur during periods of rapid growth, pregnancy, gastrointestinal upsets, and infections. Individuals exhibit differences in their ability to assimilate and metabolize vitamins and in their ability to store or destroy them.

It is with some surprise that people react to the idea of a nationwide malnutrition in a country of supposed plenty and surplus. But when we are told that half of the people of this country live on less than twenty-five cents a day for food, it becomes obvious that the problem involves economics to a marked degree. However, it also involves food habits which, while correctable, are as a rule changed with difficulty. The bulk of the caloric intake is in the form of white flour, sugar, and fat. The thing that needs to be done is to reenforce these staples of our diet so that all people will have access to a sufficient amount of the protective substances.

Some constructive work has already been done by the addition of vitamin B factors and iron to white flour, as recommended by the Committee on Foods and Nutrition of the National Research Council. Edible fats, such as margarine and lard, are also made to have much greater nutritional value if reenforced with vitamins A and D. Skim milk solids need to be put to much better use because they contain valuable nutritives in the form of proteins and calcium. The per capita consumption of sugar in this country has been ap-

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**Lq Cellule*, 1901, chap. XVIII.

The potency of vitamins A and D when appearing on a label must be in U. S. P. units, but the vitamin content of ascorbic acid, thiamine, riboflavin, nicotinic acid, nicotinamide, pyridoxine, menadione, and other vitamin K preparations when expressed must be in terms of milligrams.*

The Council has also taken steps to discourage the buying and use of large doses of vitamins which often bear no relationship to established therapeutic doses or to normal requirements. Consideration for acceptance is made by the Council of various multivitamin preparations providing the content is in proportion to daily needs for such vitamins.

Vitamin A

Vitamin A, the fat-soluble, growth-promoting vitamin, is essential for growth in the young and for the maintenance of health at all ages. The chemistry of this vitamin has been established. It is related to the carotinoid pigments of plants, especially to carotene. In fact the term *vitamin A* may be applied to vitamin A, alpha-carotene, beta-carotene, gamma-carotene, and cryptoxanthin. The last four bodies are formed in plants and are precursors of vitamin A in the body.

The chemical properties of carotene and vitamin A are:

CAROTENE	VITAMIN A
Synthesized in plant.	Stored in animal.
Orange-red in color.	Almost colorless.
No selective absorption in vicinity of 3280 A.	Marked absorption at 3280 A.
Greenish-blue color with antimony tri-chloride, with maximum at 5900 A.	Vivid blue color with antimony tri-chloride, showing maxima at 5270 and 6060 A.

Using these tests, chemists have failed to detect vitamin A in any plant foodstuff. The carotene of plants, therefore, seems to supply the provitamin, from which the body prepares vitamin A. The amount of chlorophyll in the plant is a rough indication of the amount of carotene present.

Physiologic Function.—Vitamin A has at least two important uses in the body. One is related to vision and the prevention of night blindness and the other is related to the maintenance of health of epithelial cells in the body.

Absorption of Vitamin A.—Vitamin A and also carotene are readily absorbed from the normal gastrointestinal tract. Due to the fact that this vitamin and its precursors are fat soluble their absorp-

*N. N. R., 1947, p. 486.

proximately 5½ ounces daily.* White sugar contains no vitamins and no minerals, hence its extensive use becomes a nutritional error. It has been suggested that some of the skim milk solids be combined with the sugar and in this way solve some of the skim milk as well as the sugar problems.*

If the program for the reenforcement of our staple foods can be effectively carried out, a great step will be taken toward creating a nutritional environment which can then be easily supplemented with other foods chosen to round out the diet.

Present Status of Vitamins.—Because potent vitamin concentrates are now available, it is possible to prescribe exact dosage of preparations in pure form rather than rely entirely on foods rich in the required vitamin. This has materially enriched the clinical knowledge about vitamins by making possible specific therapy for deficiency conditions and a more accurate evaluation of the concentrate. In some instances measurement of the vitamin concentration of the blood has been possible.

The rather easy availability of vitamin preparations has led to certain abuses. The preparation and use of expensive vitamin mixtures which do not have a rational therapeutic use have been condemned by the Council on Pharmacy and Chemistry.† There is no evidence at present that vitamins are of value for disease unless that disease is accompanied by some degree of vitamin deficiency.‡

From little understood dietary entities, vitamins have developed into definite chemical substances whose physiologic and therapeutic activities have been the subject of rather intensive study. This justifies their being given consideration as drugs.

Vitamin Potency

The U. S. P. units for vitamins A, B, C, and D are identical in value with the International units. The Council on Pharmacy and Chemistry has decided that when practicable the vitamin content of preparations should be stated in milligrams in preference to micrograms or units. This is to help prevent the spread of misinformation about the potency of preparations. Since a milligram is equal to 1,000 micrograms, expression of vitamin content in terms of micrograms may be misleading.

*Wilder, Russell M.: Nutrition in the United States. A Program for the Present Emergency and the Future, *Ann. Int. Med.* 14: p. 2196, 1941.

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proximately 5½ ounces daily.* White sugar contains no vitamins and no minerals, hence its extensive use becomes a nutritional error. It has been suggested that some of the skim milk solids be combined with the sugar and in this way solve some of the skim milk as well as the sugar problems.*

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Present Status of Vitamins.—Because potent vitamin concentrates are now available, it is possible to prescribe exact dosage of preparations in pure form rather than rely entirely on foods rich in the required vitamin. This has materially enriched the clinical knowledge about vitamins by making possible specific therapy for deficiency conditions and a more accurate evaluation of the concentrate. In some instances measurement of the vitamin concentration of the blood has been possible.

The rather easy availability of vitamin preparations has led to certain abuses. The preparation and use of expensive vitamin mixtures which do not have a rational therapeutic use have been condemned by the Council on Pharmacy and Chemistry.† There is no evidence at present that vitamins are of value for disease unless that disease is accompanied by some degree of vitamin deficiency.‡

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foods, on the other hand, usually contain both the vitamin and one or more of the precursors.

Dietary Requirement.—It has been conclusively established that the vitamin A daily requirement is a rather large one, if optimum conditions of nutrition are to be maintained. Vitamin A requirement is particularly high during periods of rapid growth, pregnancy, lactation, and also in certain disease conditions in which body capacity for adequate absorption and utilization is impaired. The minimal requirement for the average man (70 Kg.) has been estimated to be from 1750 to 3850 international units per day when vitamin A itself is given.¹ Experimentation, however, has shown that increasing benefits have been obtained in laboratory animals as the vitamin A content is increased up to four times that of the minimal requirement.² Most authorities recommend 5000 to 6000 I.U. daily for growing children and pregnant women.

Preparations.—

Cod Liver Oil (Oleum Morrhuæ), U. S. P. Partially destearinated. Dosage: 8 cc. (2 fluidrams) orally. Cod Liver Oil contains in each gram not less than 850 U. S. P. units of vitamin A and not less than 85 U. S. P. units of vitamin D.

Nondestearinated Cod Liver Oil (Oleum Morrhuæ Non-Destearinatum), U. S. P. Dosage: 8 cc. (2 fluidrams) orally. Contains not less than 850 U. S. P. units of vitamin A and 85 U. S. P. units of vitamin D per gram.

Emulsion of Cod Liver Oil (Emulsum Olei Morrhuæ), U. S. P. Dosage: Infants and adults 15 cc. (4 fluidrams). This is cod liver oil (50%) with acacia, syrup, methyl salicylate, and distilled water.

Halibut Liver Oil (Oleum Hippoglossi), U. S. P. Dosage: 6-10 drops daily for infants; 15-20 drops for rapidly growing infants or those with vitamin deficiency. Halibut liver oil contains in each gram not less than 60,000 U. S. P. units of vitamin A and not less than 600 U. S. P. units of vitamin D.

Percomorph Liver Oil, N. N. R. Dosage: Ten drops daily for normal infants; 20 drops daily for severe deficiency. Percomorph oil is biologically assayed to have not less than 60,000 U. S. P. units per gram of vitamin A and not less than 8,500 U. S. P. units of vitamin D per gram.

¹Sherman, H. C.: *Chemistry of Food and Nutrition*, New York, 1941. The Macmillan Co., p. 421.

²MacLeod, G., and Taylor, C. M.: *Rose's Foundations of Nutrition*, New York, 1944. The Macmillan Co., p. 220.

tion is related to the ability of the body to absorb fat. Efficient absorption is therefore dependent on the presence of adequate bile salts in the intestine. Certain conditions such as obstructive jaundice, some infectious diseases, and the presence of mineral oil in the intestine may result in a definite deficiency of vitamin A in spite of the fact that the ingestion by mouth was normal.

Storage and Excretion.—Vitamin A is stored in the liver to a greater extent than elsewhere. The liver also functions in changing carotene to vitamin A. This function is inhibited in certain diseases of the liver and also in diabetes. The amount of vitamin A stored in the liver depends upon the dietary intake. When the intake is high or even excessive, the stores formed in the liver may become sufficient to last for a long time. Vitamin A is lost chiefly by destruction. Little is lost through the ordinary channels of excretion.

The Biologic Assay of Vitamin A.—Albino rats are brought to a condition of avitaminosis by feeding a diet lacking in vitamin A, or provitamin A. The amount of material containing vitamin A necessary to produce a certain standard growth response is determined. The International Unit of vitamin A is the growth-promoting activity of 0.0006 mg. of crystalline beta-carotene. This is also the U. S. P. unit.

Therapeutic Uses of Vitamin A.—Vitamin A is used in the treatment or relief of symptoms associated with a vitamin A deficiency (avitaminosis) which are night blindness (nyctalopia), keratinization of epithelial cells, retarded growth, xerophthalmia, keratomalacia, weakness, increase of susceptibility of mucous membranes to infection.

The widespread use of vitamin A preparations to prevent upper respiratory infections in the winter is, however, open to question when they are given to a patient whose diet is already adequate. The diet low in vitamin A should be corrected with foods rather than with drugs. However, it appears that large doses of vitamin A may be given with no apparent harm to the individual.

There are times when vitamin A concentrates have a legitimate use as supplements to the diet. They are during pregnancy and lactation, in infancy, or in conditions where the absorption and storage of vitamin A are not normal.

The important sources of vitamin A are the green and yellow vegetables, such as broccoli, parsley, spinach, green lettuce, carrots, and sweet potatoes, as well as egg yolk, butter, cream, ice cream, and cream cheeses.

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Cod Liver Oil (Oleum Morrhuæ), U. S. P. Partially destearinated.

Dosage: 8 cc. (2 fluidrams) orally. Cod Liver Oil contains in each gram not less than 850 U. S. P. units of vitamin A and not less than 85 U. S. P. units of vitamin D.

Nondestearinated Cod Liver Oil (Oleum Morrhuæ Non-Destearinatum), U. S. P. Dosage: 8 cc. (2 fluidrams) orally. Contains not less than 850 U. S. P. units of vitamin A and 85 U. S. P. units of vitamin D per gram.

Emulsion of Cod Liver Oil (Emulsum Olei Morrhuæ), U. S. P. Dosage: Infants and adults 15 cc. (4 fluidrams). This is cod liver oil (50%) with acacia, syrup, methyl salicylate, and distilled water.

Halibut Liver Oil (Oleum Hippoglossi), U. S. P. Dosage: 6-10 drops daily for infants; 15-20 drops for rapidly growing infants or those with vitamin deficiency. Halibut liver oil contains in each gram not less than 60,000 U. S. P. units of vitamin A and not less than 600 U. S. P. units of vitamin D.

Percomorph Liver Oil, N. N. R. Dosage: Ten drops daily for normal infants; 20 drops daily for severe deficiency. Percomorph oil is biologically assayed to have not less than 60,000 U. S. P. units per gram of vitamin A and not less than 8,500 U. S. P. units of vitamin D per gram.

¹Sherman, H. C.: *Chemistry of Food and Nutrition*, New York, 1941, The Macmillan Co., p. 421.

²MacLeod, G., and Taylor, C. M.: *Rose's Foundations of Nutrition*, New York, 1944, The Macmillan Co., p. 220.

tion is related to the ability of the body to absorb fat. Efficient absorption is therefore dependent on the presence of adequate bile salts in the intestine. Certain conditions such as obstructive jaundice, some infectious diseases, and the presence of mineral oil in the intestine may result in a definite deficiency of vitamin A in spite of the fact that the ingestion by mouth was normal.

Storage and Excretion.—Vitamin A is stored in the liver to a greater extent than elsewhere. The liver also functions in changing carotene to vitamin A. This function is inhibited in certain diseases of the liver and also in diabetes. The amount of vitamin A stored in the liver depends upon the dietary intake. When the intake is high or even excessive, the stores formed in the liver may become sufficient to last for a long time. Vitamin A is lost chiefly by destruction. Little is lost through the ordinary channels of excretion.

The Biologic Assay of Vitamin A.—Albino rats are brought to a condition of avitaminosis by feeding a diet lacking in vitamin A, or provitamin A. The amount of material containing vitamin A necessary to produce a certain standard growth response is determined. The International Unit of vitamin A is the growth-promoting activity of 0.0006 mg. of crystalline beta-carotene. This is also the U. S. P. unit.

Therapeutic Uses of Vitamin A.—Vitamin A is used in the treatment or relief of symptoms associated with a vitamin A deficiency (avitaminosis) which are night blindness (nyctalopia), keratinization of epithelial cells, retarded growth, xerophthalmia, keratomalacia, weakness, increase of susceptibility of mucous membranes to infection.

The widespread use of vitamin A preparations to prevent upper respiratory infections in the winter is, however, open to question when they are given to a patient whose diet is already adequate. The diet low in vitamin A should be corrected with foods rather than with drugs. However, it appears that large doses of vitamin A may be given with no apparent harm to the individual.

There are times when vitamin A concentrates have a legitimate use as supplements to the diet. They are during pregnancy and lactation, in infancy, or in conditions where the absorption and storage of vitamin A are not normal.

The important sources of vitamin A are the green and yellow vegetables, such as broccoli, parsley, spinach, green lettuce, carrots, and sweet potatoes, as well as egg yolk, butter, cream, ice cream, and cream cheeses.

Our plant foods usually contain no vitamin A as such, but owe their vitamin A value to the precursors which they contain. Animal

fied, and synthesized.* There is evidence of a number of additional compounds which belong to the complex. The factors are water-soluble.

Thiamine (vitamin B₁) the antiberiberi vitamin and the one which prevents polyneuritis in man.

Riboflavin (vitamin G or more recently vitamin B₂).

Nicotinic acid (niacin) (P-P) factor, deficiency of which causes pellagra.

Pyridoxine (Vitamin B₆) a factor for which there is no satisfactory evidence that it has therapeutic significance for man, but it does prevent nutritional dermatosis in rats.

Pantothenic acid, a factor which prevents nutritional dermatosis in chicks and is necessary for normal growth in rats, but its value in human nutrition is undetermined.

Biotin, although its formula is known, its therapeutic significance has not been determined.

Folic acid, a factor which is effective in the treatment of pernicious anemia. Vitamin B₁₂ and "Norite eluate factor" are closely related to folic acid.

THIAMINE HYDROCHLORIDE, U. S. P.

Thiamine (Vitamin B₁) was adopted by the Council on Pharmacy and Chemistry as the name for crystalline vitamin B chloride. There is evidence that thiamine is essential in the intermediary steps of the metabolism of carbohydrates. It is needed for the normal functioning of the nervous, cardiovascular, and digestive systems.

Symptoms of Deficiency.—Thiamine deficiency is recognized as being of fundamental importance in beriberi. This disease still kills large numbers of people throughout the world. In its milder forms it is not of infrequent occurrence in the United States.† The symptoms of thiamine deficiency are particularly related to the nervous and cardiovascular systems: loss of muscle strength, polyneuritis, disturbances of sensation, tender nerve trunks, irregularities of heart action, loss of appetite, dyspnea, and epigastric disorders.

Milder forms of deficiency may be seen any place where economic stress is sufficient to limit the thiamine intake or where food habits are such that the thiamine intake is insufficient. The symptoms may consist of loss of appetite, weakness, muscular aches and pains, decreased blood pressure, tachycardia, irritability, and mental depression.

*New and Nonofficial Remedies, 1947, p. 489.

†Goodman and Gilman: The Pharmacological Basis of Therapeutics, The Macmillan Co., p. 1247.

Shark Liver Oil, N. N. R. Dosage: One capsule or about 0.52 cc. daily. Shark liver oil is assayed to have a potency of not less than 16,500 U. S. P. units of vitamin A or less than 40 U. S. P. units of vitamin D per gram.

Oleovitamin A (*Oleovitamina A*; Natural Vitamin A in Oil), U. S. P. This is either fish liver oil alone or fish liver oil diluted with vegetable oil, or a solution of vitamin A concentrate in fish liver oil or vegetable oil. Each gram contains not less than 50,000, and not more than 65,000 U. S. P. units of vitamin A, and not more than 1000 U. S. P. units of vitamin D. Average daily dose: Infants and adults, 0.1 c.c. ($1\frac{1}{2}$ minims).

Oleovitamin A Capsules (*Capsulae Oleovitaminae A*), U. S. P. Dosage: 1 capsule containing 5000 U. S. P. units of vitamin A.

Oleovitamin A and D (*Oleovitamina A et D*), U. S. P. Dosage: Infants and adults 8 cc. (2 fluidrams). Contains in each gram not less than 850 and not more than 1100 U. S. P. units of vitamin A and not less than 85 and not more than 110 U. S. P. units of vitamin D.

Concentrated Oleovitamin A and D (*Oleovitamina A et D Concentrata*), U. S. P. Dosage: Prophylactic, infants and adults 0.1 cc ($1\frac{1}{2}$ minims). Contains in each gram not less than 50,000 and not more than 65,000 U. S. P. units of vitamin A and not less than 10,000 or more than 13,000 U. S. P. units of vitamin D.

Cod Liver Oil Concentrates, N. N. R. Cod Liver Oil Concentrates are available in bottles, vials, capsules, and tablets. They are available in strengths up to 60,000 units of vitamin A and 8,500 units of vitamin D per gram. The concentrates are more expensive than the cod liver oil.

Carotene (Pro-vitamin A), N. N. R. Carotene is usually administered in the form of carotene dissolved in an oily solution. This is biologically assayed to have in each gram a vitamin A potency of not less than 7,500 units U. S. P. Excessive doses should be avoided to prevent carotenemia. Liquid petrolatum should not be given together with preparations of carotene.

Vitamin B Complex

The term "vitamin B complex" refers to a group of substances which are constituents of what was formerly called vitamin B. Research has shown an ever-changing picture of the constituents of this complex. At present eight compounds have been isolated, identi-

Thiamine Hydrochloride (Thiaminae Hydrochloridum), U. S. P. Dosage: Determined by the physician according to the needs of the patient.

Thiamine Hydrochloride Tablets (Tabellae Thiaminae Hydrochloridum), U. S. P.

Extract of Rice Polishings (Extractum Perpolitionum Oryzae), U. S. P. Dosage: 8 cc. (2 fluidrams). This contains in each cubic centimeter not less than 20 U. S. P. units of Vitamin B₁ and represents not less than 14.5 Gm. of rice polishings.

RIBOFLAVIN, U. S. P.

Vitamin B₂, Riboflavin or Lactoflavin.—Crystals of riboflavin are of an orange yellow color and are soluble in water. Thiamine contains sulfur; riboflavin does not. Riboflavin was first identified in milk. Later it was identified in other substances and was called lactoflavin because of its intense yellow color. Its relationship to the vitamin B complex was not appreciated until it was observed that concentrates of the vitamin B₂ (G) had a yellow color, the intensity of which was related to the potency of the concentrate. At present the vitamin B₂ is synthesized and all doubt of its identity has been removed.

Riboflavin seems to function in cell respiration and is a constituent, apparently, of all cells. It is water-soluble and heat-stable.

Symptoms of Deficiency.—Symptoms of deficiency have been observed in both laboratory animals and human beings. Rats develop a type of nonspecific dermatitis, lose hair, age prematurely, and may develop cataracts. In human beings superficial fissures about the angles of the mouth and nose, disturbances of vision and changes in tissues of the eye may develop. It has also been shown that the riboflavin content of the diet affects the susceptibility of laboratory animals to rickettsial diseases.¹

Dietary Sources.—Milk is normally the most important source of riboflavin. Other sources of riboflavin are liver, kidney, eggs, and lean meat. Wheat germ, kale, spinach, and broccoli are good plant sources.

Riboflavin Requirements.—It is thought advisable to keep the body saturated with riboflavin, and therefore the optimum intake of this vitamin is well above the minimum requirement. The optimum intake for an infant is thought to be about 1 mg. per day and for an adult 3 mg. per day.² The requirement during lactation and preg-

¹Sherman, H. S.: *Chemistry of Food and Nutrition*, New York, 1941, The Macmillan Co., p. 374.

²N. N. R., 1947, p. 511.

Human Requirements.—It has been estimated that adults require approximately 1 mg. of thiamine chloride daily, with an optimum intake of 1.5 to 2.5 mg. For the child 0.03 mg. per 100 calories is considered optimum.* The requirements are increased during pregnancy and lactation, when the metabolic rate is elevated or when the body is unable to absorb or utilize the vitamin. It is stored in the body to a limited extent, being found chiefly in the liver, brain, kidney, and heart. The amount that is stored is directly related to the intake. It is found to some extent in all body tissues.

There is no evidence that doses of thiamine greatly in excess of the therapeutic ones cause toxic effects.†

Therapeutic Uses.—In conditions of vitamin deficiency it may be advisable to administer several components of the vitamin B complex. This is best accomplished by an adequate diet or preparations rich in the B factors, such as yeast. In other instances thiamine is indicated as in beriberi, forms of polyneuritis, and for the relief of symptoms which accompany the milder forms of thiamine deficiency.

Foods Rich in Vitamin B₁.—Whole grain cereals and bread, egg yolk, liver, leafy vegetables, yeast. Heating and cooking reduce the vitamin content.

PREPARATIONS

To supplement the diet, use compressed yeast tablets, 1 to 20 Gm. daily; yeast extracts or concentrates, 12-24 cc. for adults, thiamine chloride (synthetic B₁), 1 cc. ampules contain 3000 units. Thiamine tablets are procurable with units stated on the container. One unit of thiamine chloride is defined as the amount of biological activity in .003 mg. of vitamin B₁ hydrochloride.

Dried Yeast (*Saccharomyces Siccum*), U. S. P. Dosage: Determined by the physician according to the needs of the patient. Dried yeast must contain in each gram not less than 0.12 mg. of thiamine hydrochloride, 0.04 mg. of riboflavin, and 0.25 mg. of nicotinic acid.

Dried Yeast Tablets (*Tabellae Saccharomycitis Sicci*), U. S. P. Dosage: As prescribed. This preparation must contain at least 95 per cent of the labelled amount of dried yeast.

Triasyn, U. S. P. Triasyn B capsules and tablets contain not less than 2 mg. thiamine hydrochloride, 3 mg. riboflavin, and 20 mg. nicotinamide. Dose determined by physician.

*N. N. R., 1947, p. 506.

†N. N. R., 1947, p. 507.

suffering from a niacin deficiency are quite likely to suffer from other vitamin deficiencies as well, and do not become well merely by increasing the niacin intake. What is needed is an all around more adequate diet. Large doses of nicotinic acid are likely to cause symptoms of overdosage, especially when given intravenously. It produces flushing of the face and neck and an unpleasant sensation. Nicotinamide is the preparation of choice for parenteral administration.

Preparations.—

Nicotinic Acid (Acidum Nicotinicum), U. S. P. (Niacin). Dosage: 25 mg. ($\frac{3}{8}$ gr.) orally.

Nicotinic Acid Tablets (Tabellae Acidi Nicotinici), U. S. P. Dosage: 25 mg. ($\frac{3}{8}$ gr.) orally.

Nicotinamide Injection (Inj. Nicotinamidum), U. S. P. Dosage: 100 mg. ($1\frac{1}{2}$ gr.) parenterally.

Nicotinamide Tablets (Tabellae Nicotinamidi), U. S. P. Dosage: 25 mg. ($\frac{3}{8}$ gr.).

PYRIDOXINE (VITAMIN B₆), N. N. R.

Pyridoxine is a pyridine derivative related to nicotinic acid. It appears to be connected with the utilization of unsaturated fatty acids. Its function in human nutrition is still under investigation. "It has been accepted by the Council for purposes of standardization and experimentation only."* Dosage: 5 to 10 mg. daily is suggested.

FOLIC ACID, N. N. R.

The chemical name of the synthesized folic acid compound is Pteroyl glutamic acid. It has been found useful in the treatment of pernicious anemia and for certain other macrocytic anemias found in man. It is found in the free form in a large number of foods but in very small quantities. To what extent the body is able to utilize folic acid in a combined form is not fully understood.

Action.—Folic acid brings about a response of the blood similar to that produced by liver extract although apparently it does not prevent or arrest changes in the spinal cord. It is therefore used along with liver rather than as a substitute for liver.

Administration and Dosage.—Folic acid is given in oral doses of 5 to 10 mg. daily. It may be given intramuscularly but there seems to be no advantage in giving it parenterally.

*N. N. R., 1947, p 516.

nancy is higher. When riboflavin is used therapeutically, 2 to 10 mg. per day may be given, depending upon the amount of deficiency. No side effects have been reported.

Preparations.—

Riboflavin Injection (Lactoflavin, Vitamin B₂, Vitamin G), U. S. P. Dosage determined by physician in accordance with the patient's needs. Available in strengths of 0.2 mg. to 5 mg. per cc.

Riboflavin Tablets (Tabellae Riboflavini), U. S. P. Riboflavin tablets are available in amounts of 1 and 5 mg. per tablet.

Yeast preparations are also given for their riboflavin content.

Therapeutic Uses.—Riboflavin is recommended for use in the alleviation of symptoms of deficiency encountered in—

1. Pellagra.

2. Certain conditions of the eye characterized by itching, burning, photophobia, and a sensation of roughness of the eyes (keratitis).

3. Certain lesions of the tongue, lips, and face, with the development of cheilosis, follicular keratosis, at the naso labial fold, over the nose and on the forehead.

NICOTINAMIDE (NICOTINIC ACID), U. S. P.

Nicotinic Acid.—Nicotinic acid is chemically related to nicotine but possesses none of the latter's pharmacologic properties. This compound is a dietary essential, the lack of which is responsible for the symptoms of pellagra, which are characterized by disturbances of the gastrointestinal tract, skin, and nervous system. In a milder degree of deficiency, patients are nervous, irritable, have indigestion, diarrhea or constipation, and frequently a certain amount of skin pigmentation.

Therapeutic Uses.—Nicotinic acid and nicotinamide are considered specifics only in the treatment of pellagra. They alleviate many of the symptoms of pellagra but do not affect those symptoms due to a deficiency of thiamine or riboflavin.

Dietary Sources.—Foods rich in nicotinic acid or niacin are milk, liver, lean meats, fish, eggs, tomatoes, green and leafy vegetables such as kale, mustard greens, and collards.

Nicotinic Acid Requirement.—The optimum intake of nicotinic acid has not been established conclusively. For adults it seems to be between 15 and 20 mg. per day. The maximum dose when given therapeutically is 500 mg. per day in divided doses.¹ Individuals

¹N. N. R., 1947, p 513.

Vitamin D

Vitamin D is a term applied to two or more substances which affect the proper utilization of calcium and phosphorus in the body. Two forms of naturally occurring vitamin D have been isolated. One of these forms is obtained as one of the products of irradiated ergosterol and is known as D₂ or calciferol. Ergosterol has therefore been shown to be a precursor of vitamin D. Investigation has further shown that there are a number of precursors which by irradiation can be changed into compounds which have vitamin D activity. Irradiation of 7-dehydro-cholesterol results in the formation of vitamin D₃ and is the form of vitamin found in irradiated milk and in a number of fish oils. It is also formed in the skin when an individual is exposed to sunlight. Irradiated ergosterol (calciferol) is the active constituent in various vitamin preparations such as viosterol, irradiated yeast, etc.*

Vitamin D₂ and Vitamin D₃ as well as other products of irradiated ergosterol are capable of antirachitic activity.

Therapeutic Action.—The exact mechanism by which vitamin D functions in the metabolism of calcium and phosphorus is not known. It seems to be directly concerned with the absorption of calcium and phosphorus from the intestinal tract. In the absence of vitamin D, the amount of these substances absorbed from the bowel is diminished to such an extent that even though the calcium and phosphate intake is adequate, rickets results.

An enzyme called phosphatase exists in the body and is closely related to phosphorus metabolism. It is widely distributed in the animal body but particularly active in ossifying cartilage. When rickets is present the value for the phosphatase in the blood serum is high. This is thought to be due to leakage from the diseased bone. Administration of vitamin D causes the enzyme to return slowly to normal.

Symptoms of Vitamin D Deficiency.—The chief symptoms and signs indicating the use of vitamin D are rickets, indicated by irritability, craniotabes, prominent frontal bosses, delayed closing of the fontanels, soft bones, pigeon breast, rachitic rosary, flaring ribs, epiphyseal enlargement at wrists and elbows, muscular weakness, protruding abdomen, bowed legs, delayed eruption of teeth, abnormal ratio of calcium and phosphorus in the blood, and perhaps infantile tetany. Adult rickets is known as osteomalacia.

Dietary Sources.—Although vitamin D is an essential vitamin, it is contained in only a few foods of the average American diet.

*Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 1261.

ASCORBIC ACID (VITAMIN C) (CEVITAMIC ACID)

Scurvy was formerly common among sailors when deprived of fresh vegetables during long voyages. The well-known effects of lemon and orange juices in curing this disease led to attempts to concentrate the active principle by chemical means. Crystalline cevitic acid or ascorbic acid in large amounts has been prepared from Hungarian red pepper. Biological tests show that ascorbic acid is pure vitamin C. It is now synthesized on a commercial scale. Ascorbic acid is a powerful reducing agent and is therefore sensitive to oxidation. It is relatively stable in an acid medium but quickly oxidized in an alkaline medium. It is believed to be concerned in the oxidation-reduction reactions of all living cells. In addition, it is concerned with the formation of collagen of all fibrous tissue including bone, and with normal development of teeth, blood vessels, and blood cells.

Deficiency Symptoms.—A deficiency in the intake of vitamin C results in scurvy the chief symptoms of which are spongy bleeding gums, loosened teeth, hemorrhagic tendencies in regions subjected to trauma or mechanical stress, sore swollen joints, fatigue, pallor, and anemia. Vitamin C deficiency is thought to be a contributory factor in dental caries, pyorrhea, and certain mouth infections.

Dietary Sources.—Foods rich in vitamin C include citrus fruits, oranges, lemons, limes, grapefruit, as well as tomato juice, raw cabbage, onions, spinach, and lettuce.

Therapeutic Uses.—The specific therapeutic use of vitamin C is in the prevention and treatment of scurvy. An optimum amount of ascorbic acid should be supplied at all ages to prevent the development of scurvy. It is not considered specific in the treatment of pyorrhea, dental caries, certain gum infections, etc., unless these symptoms are clearly associated with a vitamin C deficiency.

Requirements.—The optimum daily intake of ascorbic acid for an infant appears to be about 30 mg. and that for an adult approximately 75 mg.¹ During pregnancy and lactation the requirement is greater. Therapeutic doses of 100 to 150 mg. daily may be given without undesirable effects.

Preparation.—

Ascorbic Acid (Acidum Ascorbicum), U. S. P. (Cevitic Acid).

Dosage: Determined in accordance with patient's needs. Tablets available in 25, 50, and 100 mg. amounts.

Sodium Ascorbate Injection, U. S. P., possesses the activity of ascorbic acid and is preferred for parenteral therapy.

¹N. N. R., 1947, p. 518.

3. Patients suffering from bone fractures, especially elderly individuals, may benefit from the administration of vitamin D, thus promoting optimum conditions for the healing of bone.

4. Vitamin D may be administered in a number of conditions, such as arthritis, psoriasis, diarrhea, steatorrhea, etc., if there is good evidence that a deficiency of this vitamin exists.

Preparations.—

Many of the official preparations containing vitamin A and vitamin D have been listed under preparations of vitamin A. In addition, are listed preparations of irradiated ergosterol.

Synthetic Oleovitamin D (Oleovitamina D Synthetica), U. S. P. (Viosterol in Oil). Dosage: Prophylactic 0.1 cc. (1½ minims). In severe cases doses in excess of 1.5 cc. (20 minims) may be given. This is a solution of activated ergosterol or activated 7-dehydrocholesterol, in an edible vegetable oil, and contains not less than 10,000 U. S. P. units of vitamin D in each gram.

Blended Oil Containing Vitamins A and D, N. N. R. A mixture of fish and/or vegetable oils to which Viosterol may be added. The vitamin A content is not less than 1,800 U. S. P. units per gram and the vitamin D content not less than 175 U. S. P. units per gram.

This is fish and/or vegetable oils to which Viosterol is added to assure the adequate U. S. P. potency of vitamin D per gram.

Multiple Vitamin Preparations.—

Hexavitamin Capsules (Capsulae Hexavitaminarum), U. S. P.

Hexavitamin Tablets (Tabellae Hexavitaminarum), U. S. P.

The above capsules and tablets each contain the following: Not less than 5000 U. S. P. Units of vitamin A from natural (animal) sources, 400 U. S. P. Units of vitamin D from natural (animal) sources, or as activated ergosterol or activated 7-dehydrocholesterol, 75 mg. of ascorbic acid, 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin, and 20 mg. of nicotinamide. (These preparations thus contain vitamins A, B₁, B₂, C, D, and Niacin.)

Dosage: As prescribed, and according to the patient's needs.

In addition, there are numerous proprietary preparations of multiple vitamins of which Multicebrin (Lilly) is an example. The label states that each gelseal contains 3 mg. of thiamin chloride; 2 mg. of

Small amounts are present in herring, sardines, salmon, tuna fish, and eggs. Butter contains only a small amount of vitamin D.¹

Human Requirement.—It is thought that either the human requirement of vitamin D is relatively low or else it is met by the action of sunlight on the skin. During pregnancy and lactation and for young children (under 1 year) 400 to 800 international units of vitamin D are the daily requirement recommended by the Food and Nutrition Board of the National Research Council.²

Older children and adults who live in a climate where they do not have access to abundant sunshine also need to supplement their vitamin D intake. The amount supplied should probably be up to the minimum requirements for the infant. To prevent the development of rickets, it is important to start the administration of vitamin D early in the infant's life, and full dosage should be given by the second month.

Toxicity.—Certain pathologic changes have been noted in animals after the administration of huge doses of vitamin D but it is thought that toxic reactions in human beings may have been due in the past to toxic irradiation products. No serious toxic symptoms have been reported in cases where many times the therapeutic dose has been given. On the other hand, some adults have complained of nausea, vomiting, headache, diarrhea, lassitude, and urinary infrequency, after large doses of vitamin D. Elevation of the serum calcium above 12 mg. per 100 cc. is considered a danger signal; dosage should be reduced or temporarily discontinued.

Therapeutic Uses.—

1. The prevention of rickets in young children is one of the most justified uses of vitamin D. The initial dose should be about 200 units daily with an increase in dosage up to 800 units by the second month. Premature infants or those who seem to be especially susceptible to the development of rickets need a larger intake (800-1200 units usually). When children already have rickets the dosage is also greater. The average daily dose is usually about 1200 units but in some instances may be increased to as much as 60,000 units daily. If nausea or anorexia appear, the vitamin should be temporarily discontinued.

2. Adult rickets or osteomalacia also calls for large doses of vitamin D, along with improved dietary conditions.

¹American Medical Association Council on Foods and Nutrition. Handbook of Nutrition; A symposium, Chicago, 1943, p. 137.

²Ibid., p. 138.

and serum proteins are gradually lost into the tissues, resulting in the formation of edema and a lowering of the blood protein.

The clinical significance of this vitamin awaits determination.

HORMONES AND AUTOPHARMACOLOGY

Hormones are chemical substances produced by the ductless glands. The word hormone comes from the Greek word (hormon) meaning to excite. Chalones are chemical substances which cause depression of a function. Both chalones and hormones might be considered the active principles of secretions of the endocrine glands. Autopharmacology is a study of the action of substances produced by the body itself.

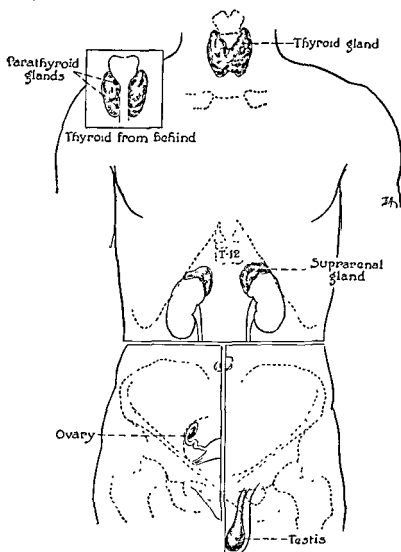


FIG. 33—Location of some of the glands of internal secretion. Why are these structures often called ductless glands? (From McClendon and Pettibone: *Physiological Chemistry*, The C. V. Mosby Co.)

riboflavin, 20 mg. nicotinamide, 1 mg. pyroxidine hydrochloride, 1 mg. of pantothenic acid, 50 mg. ascorbic acid, 5000 U. S. P. units of vitamin A and 500 U. S. P. units of vitamin D.

Vitamin E

Vitamin E is known as a fat-soluble, antisterility vitamin. A number of compounds have been found which exhibit vitamin E activity. The most active of these compounds are the tocopherols. These chemical substances are readily soluble in fat solvents, resist high temperatures, and lose their activity in the presence of mild oxidizing agents.

It has never been demonstrated that a deficiency of vitamin E occurs in man. In animals a lack of vitamin E manifests itself by changes in the reproductive mechanism and by changes in the muscular and nervous systems. It is said to cause changes in the germ cell in the male and death of the embryo in the female when the animals are fed on a diet deficient in vitamin E. Absence of vitamin E in the diet of rabbits and guinea pigs is followed by muscular dystrophy and paralysis of the hind quarters.

Vitamin E has been used in an effort to prevent abortions and in the treatment of a number of myoneurogenic disturbances but the interpretation of the results is a subject of controversy.

Sources.—Wheat germ oil is the richest source of vitamin E, but it is also found freely in other vegetable oils from the germs of seeds—cottonseed oil and peanut oil, as well as in lettuce and other leafy vegetables, milk, eggs, whole grain cereals, and legumes.

Preparations.—Preparations of vitamin E are not official. It has been synthesized and is available as alpha-tocopherol, 3 mg. of which is equal to 4 cc. of wheat germ oil.

The dosage for alpha-tocopherol has not been established. It can be administered both by mouth and intramuscularly.

Vitamin K

Vitamin K is discussed in the chapter on the drugs related to the circulatory system, page 318.

Vitamin P

A substance distinct from vitamin C has been reported found in the rind of lemons and in paprika.¹ It is claimed that this substance, which is called citrin, affects the permeability of the capillaries. In cases of deficiency the capillary permeability is increased,

¹Rusnyak, Stefan, and Szent-Györgyi, Albert: Vitamin P. Flavonols As Vitamins *Nature* 138: 27 (July 4) 1936.

culatory disturbances, and disturbance of the central nervous system may be noticed.

Congenital thyroid deficiency results in cretinism and a deficiency in adults causes myxedema. In these conditions the basal metabolism is subnormal. Thyroid extract or thyroid hormone acts as a specific by supplying the deficient hormone.



Fig. 24.—Cretin, nineteen years old. The treatment with thyroid extract was started too late to be of benefit. (From Bard: *Macleod's Physiology in Modern Medicine*.)

The Thyroid and Other Endocrines.—The thyroid gland is an important member of the endocrine group and is affected by other endocrine glands, especially the thyrotropic factor from the anterior lobe of the pituitary. The thyroid also exerts an influence on other endocrines, i.e., the thymus, adrenals, and the gonads. Hyperthyroidism results in increased calcium excretion and also hypertrophic changes in the parathyroid.

The internal secretions pass directly into the blood stream and stimulate some organ or organs to activity. In general, their function is to regulate growth, metabolism, and the activity of the autonomic nervous system. Each gland elaborates its own special hormone or hormones, such as insulin, adrenalin, thyroxin, cortin, sex hormone, etc. The conception of hormones is growing, however, and some may arise from tissue destruction or metabolism. The stimulating action of carbon dioxide on respiration and of urea on kidney function may be cited as instances. Choline, histamine, etc., which arise by tissue destruction, may be called hormones. As a rule, however, the term hormone is restricted to the products elaborated by the ductless glands. For these, the terms internal secretions, hormones, or autocoids are now generally reserved. Gley has postulated three criteria to define an endocrine organ:

1. Anatomic-histologic: The tissues must not secrete into a duct.
2. Chemical: An active chemical substance may be isolated from the efferent blood.
3. Physiologic: The chemical substance must exert specific physiologic effects.

The outstanding hormones are adrenalin, acetylcholine, histamine, insulin, pituitrin, thyroxin, and sex hormones.

Chemically, hormones are complex organic bodies of great activity and evanescence, for they are destroyed rapidly in the body by oxidation and hydrolysis. The complex chemistry of some of them has been described in detail by Fieser.*

Thyroid Hormone

The thyroid gland secretes a colloidal substance known as thyroglobulin which is essential for proper regulation of metabolism. Thyroxin results from the hydrolysis of thyroglobulin, and Kendall (1915) found that it contained about 65 per cent iodine. Thyroxin has been found to exhibit the same physiologic effects as the original protein.

Physiologic Action.—Although the exact mechanism of action of the thyroid hormone is not known, its primary effect is on cellular metabolism. It apparently causes all cells to accelerate their rate of metabolism. This is reflected in the way tissues grow and develop. Deficiency causes not only a slowing of growth in the young but affects many reactions both in the young and in the adult; water and salt metabolism are affected, muscular inefficiency, cir-

**The Chemistry of Natural Products Related to Phenanthrene*, Am. Chem. Soc. Monograph No. 70, 1937.

the hair becomes scanty and coarse, movements sluggish, and the patient becomes hypersensitive to cold.

Hyperthyroid States.—Excessive formation of the thyroid hormone and its escape into the circulation result in a state of toxicity called thyrotoxicosis. This occurs in the condition known as exophthalmic goiter (Grave's disease), or in some forms of adenomatous goiters.



FIG. 36.—Photograph of a patient with exophthalmic goiter. Notice the exophthalmos, the facial expression, and the enlargement of the neck. What do you think should be done to treat this patient's condition? (From Meakins: *The Practice of Medicine*, The C. V. Mosby Co.)

Hyperthyroidism leads to symptoms quite different from those seen in myxedema. The metabolic rate is increased, sometimes as much as a plus 60 or more. The body temperature is frequently above normal, the pulse rate is fast, and the patient complains of

Hypothyroid States.—Hypothyroidism in the young child is known as cretinism and is characterized by cessation of physical and mental development which leads to dwarfism and idiocy. Cretins usually have thick coarse skin, a thick tongue, gaping mouth, protruding abdomen, thick short legs, poorly developed hands and feet, and weak musculature.

This condition may result from faulty development or atrophy of the thyroid gland during fetal life. Failure of development of the gland may be due to lack of iodine in the mother.



Fig. 35.—Photograph of a patient with myxedema. Notice the thick lips, the puffiness around the eyes, the coarse, scanty hair, and the dull expression. What is the cause of myxedema? (From Meakins: *The Practice of Medicine*, The C. V. Mosby Co.)

Hypothyroidism in the adult is called myxedema. Its development is usually insidious and causes a gradual retardation of physical and mental functions. There is a gradual infiltration of the skin, loss of facial lines and facial expression. The formation of a subcutaneous connective tissue causes the hands and face to appear puffy and swollen. The basal metabolic rate becomes subnormal,

Therapeutic Uses.—Thyroid extract or thyroxin are specific in the treatment of hypothyroid conditions. Patients with cretinism or myxedema will require therapy all of their lives. This dosage must be adjusted to the needs of the patient. For most patients a U. S. P. preparation of thyroid extract in tablet form is the cheapest and most convenient form and at the same time is very effective. The object of treatment of the patient with myxedema is to rid him of symptoms, not necessarily to raise the metabolic rate to normal. In the treatment of the cretin, however, it may be necessary to raise the metabolic rate to normal or above in order to insure adequate development. It is most important to start treatment of the cretin very early in life; the sooner the better which means before the child is six months old if at all possible. Otherwise both the physical and mental retardation is likely to be permanent. In myxedema mental and physical characteristics are restored and complete cure often results.

Thyroid preparations have been extensively used in the treatment of obesity. This is at best a palliative measure and is not unaccompanied by the danger of inducing severe symptoms of toxicity. Thyroid hormone or thyroid extract should be regarded as a potent substance and should never be indiscriminately used. No one should take it who is not under direct medical supervision. If the obesity is primarily due to hypothyroidism, then its use would be indicated, but most authorities agree that most obesity is due to overeating and must be cured by reducing the caloric intake. The uncontrolled use of the drug has resulted fatally.

Thyroid preparations have also been used in connection with a number of other conditions, namely, rheumatoid arthritis, rickets, various skin diseases, epilepsy, and menstrual disturbances. Although thyroid is not considered specific for these conditions, good results have been reported in some cases. It has also been used in postoperative patients with the aim of slightly increasing the metabolic rate and thereby improving circulation of blood in the body and thus preventing the formation of emboli.

Preparations.—

Thyroid (Thyroideum), U. S. P. Dosage: 60 mg. (1 grain) orally. This preparation is obtained from the cleaned, dried gland of domesticated animals that are used for food by man.

It is also prepared in tablet form; the dosage is the same—1 grain to the tablet.

feeling too warm. Other symptoms include restlessness, anxiety, emotional instability, muscle tremor and weakness, sweating, and exophthalmos.

The most satisfactory treatment is a subtotal resection of the hyperactive gland. Since these patients are usually poor operative risks, they are frequently hospitalized for a time and prepared for surgery by giving them as much mental and physical rest as possible, a diet particularly rich in carbohydrate and vitamins, and by giving them iodine. Thyroidectomy is indicated when the pulse has been slowed and the basal metabolic rate lowered to a somewhat stationery level.

The Role of Iodine in Treatment of Thyroid Conditions.—Iodine has for some time been used empirically in the treatment of toxic goiter. The response of the thyrotoxic patient is frequently remarkable. The metabolic rate falls rapidly and many of the symptoms of hyperthyroidism are relieved. Unfortunately the beneficial effect is not prolonged indefinitely. In a few weeks the symptoms are likely to reappear and may be intensified. The use of iodine and potassium iodide in the form of Lugol's solution (Strong Solution of Iodine, U. S. P., 5-10 minims daily) is indicated not only in the preoperative preparation of the patient but is also used as a diagnostic aid.

The mechanism by which iodine accomplishes its beneficial effect is not fully understood. There is reason to believe that in conditions of hyperthyroidism there is an excessive secretion of thyroid hormone which is not stored in the gland but escapes into the circulation. One explanation is that somehow iodine temporarily checks the loss of the hormone from the gland and in that way lowers the level in the blood and thus alleviates symptoms associated with hyperthyroidism.¹

Deficiency of iodine in the thyroid gland causes it to undergo tissue changes. The gland enlarges and increases the number of active cells. This noticeable enlargement is known as a simple goiter, and it is prevalent in areas of the country where the iodine content of the soil is low. It has been demonstrated that the administration of small doses of iodine in the form of iodized salt is a satisfactory prophylactic measure in preventing the development of goiter in school children. The administration of some form of iodine after the goiter has been present for some time is less successful.

¹Goodman, L. and Gilman, A. - *The Pharmacological Basis of Therapeutics*, The Macmillan Co., p. 1165

toms to their physician immediately. The nurse should also be on the alert for such warning symptoms.

Thiouracil is given by mouth. The dosage at first is 0.4 Gm. (6 gr.) given in divided doses during the day, and after the metabolic rate returns to the normal range or the symptoms subside the dosage may be lowered to 0.1 to 0.2 Gm. daily ($1\frac{1}{2}$ to 3 gr.).

Parathyroid Hormone

Lying just above the thyroid, or, in some animals, embodied in it, are a variable number of bean-shaped glands (two pairs in man) known as the parathyroids. Complete removal of the parathyroids results in acute neuromuscular symptoms known as tetany which resembles the tetany sometimes seen in young children. The tetany is invariably associated with hypocalcemia. It seems that the glands are concerned with calcium metabolism. The symptoms are: twitching spasms, or convulsions, gradual paralysis with dyspnea, and death from exhaustion. Before death there are usually gastrointestinal hemorrhages and hematemesis. At death the intestinal mucosa is congested and the calcium content of the heart, kidney, and other tissues increased.

The symptoms of tetany are relieved by the injection of parathyroid extracts, and by calcium salts.

The use of the parathyroid hormone in therapeutics is still in the experimental stage, and the only uses at present seem to be in conditions associated with low calcium content of the serum, in tetany parathyroprivia, and in infantile tetany.

The patient should be hospitalized because a frequent check on the blood calcium and phosphate levels is essential. Many disturbances of calcium metabolism are not due to disturbance of the parathyroid function, and hypoparathyroidism is the specific indication for the use of hormonal therapy.

Preparation.—

Parathyroid Injection (Injectio Parathyroidei), U. S. P. Dosage: 25 U. S. P. Units intramuscularly.

"One cc. of the Parathyroid Injection possesses a potency of not less than 100 U. S. P. Parathyroid Units, each unit representing $\frac{1}{100}$ of the amount required to raise the calcium content of 100 cc. of the blood serum of normal dogs 1 mg. within 16 to 18 hours after administration."

The Pituitary Hormones

The pituitary body (corpus pituitarium) is about the size of a pea, and occupies a niche in the sella turcica of the sphenoid bone. It is the corypheus of the endocrine orchestra. It consists of an anterior and posterior lobe and a smaller pars intermedia composed of secreting cells. The anterior part is less important from a pharmacologic point of view than the posterior, but much more important in sustaining the life of the individual. The function of the pars inter-

Thyroxin (Thyroxinum), U. S. P. Dosage: 0.5 mg. ($\frac{1}{120}$ gr.) intravenously.

Thyroxin is the active physiologic principle prepared from the thyroid gland or made synthetically.

Thyroxin should always be given at first in minimum doses and the optimum amount determined by trial.¹

Thyroxin Fraction, N. N. R. Dosage: The drug is supplied in tablets with a stated weight of thyroxin. For oral administration.

The partially purified disodium salt of thyroxin is mixed with a product of protein hydrolysis.

Symptoms of Overdosage.—The symptoms of overdosage are in general those of hyperthyroidism, viz., palpitation, tachycardia, pain over the heart, dyspnea, nervousness, insomnia, tremor, hyperglycemia, sweating, and loss of weight.

It should be remembered that symptoms come on slowly and may last a long time. It is best, therefore, to begin with a small dose and watch the patient closely. One of the first symptoms of overdosage which the nurse may have occasion to note is an increase in the pulse rate. She should always check the pulse before giving an additional dose of the drug. In some hospitals it is the rule to withhold the drug if the pulse rate has reached one hundred beats per minute. In mild cases withdrawal of the drug will result in return to the normal metabolic level. In some severe cases it is important to put the patient at rest and give sedatives such as one of the barbiturates.

THIOURACIL, N. N. R.

Thiouracil has given evidence of usefulness in the treatment of hyperthyroidism and for toxic conditions of the thyroid gland. Although it does not inactivate the thyroxin already formed by the gland, it does interfere with further formation of thyroxin. Its effects may not be apparent for several days or several weeks. The drug is useful in the preoperative treatment of patients or for those for whom surgery is contraindicated. It should be avoided, however, if the patient's symptoms can be controlled by iodine therapy.

Toxic conditions develop frequently and include fever, dermatitis, leukopenia, granulocytopenia, jaundice, and anemia. Any of these reactions necessitate stopping the drug and giving proper supportive treatment. Patients should be instructed that if they develop sore throat, a head cold, fever, or malaise they should report the symp-

¹N. N. R., 1947, p. 380.

The Growth Hormone.—It has long been known that acromegaly, giantism, and dwarfism are connected with pathology of the anterior lobe of the hypophysis. Evans, et al., have shown that regular injections of anterior pituitary extracts into rats caused growth to twice the normal size. Similar results have been obtained in dogs. Hypophysectomy causes dwarfism. The skeleton and all organs are involved. The specific use of the growth-promoting factor of the anterior pituitary is still in the experimental stage.

The Thyrotropic Hormone.—Hypophysectomy causes atrophy of the thyroid, and injections of the hormone protect against this atrophy. In normal animals, injections of anterior pituitary cause hypertrophy of the thyroid. Injection of fresh anterior pituitary extracts into young ducks caused an enlargement of the thyroid 20 to 60 times the weight of controls. Patients with anterior pituitary involvement usually have a low metabolic rate.

The Adrenotropic Hormone.—Hypophysectomy in the rat leads to atrophy of the cortex of the adrenals. Improvement is brought about by injections of aqueous alkaline extract of the anterior pituitary. It has not yet been shown that this is due to a specific hormone. Adenomatous tumors of the cortex have been produced by such injections.

The Gonad Hormones.—Van Dyke has suggested the name *hebin* (puberty) for the gonad-stimulating hormone. If the pituitary be removed before puberty, or if the gland atrophies, puberty does not occur. The gonadotropic hormones and the lactogenic hormones are more fully discussed in Chapter XIX, p. 392.

Parathyrotropic Effect.—Little is known regarding the control of the parathyroids. They may in a measure be under the influence of the anterior lobe of the pituitary. In some tumors of the hypophysis, hyperplasia of the parathyroids has been detected. A similar condition has been produced by the injection of anterior pituitary extract.

Pancreatropic Effects.—Anselmino and Hoffmann report that anterior lobe extract causes increase in number and enlargement of the islets of Langerhans in the pancreas, and a slight fall of blood sugar. From their results, they believe this hormone stimulates insulin production.

Ketogenic Effect.—Anterior pituitary extract injected into fasting rats on a diet of butter fat gives rise to acetone bodies in the blood and urine. This effect may be obtained with extracts free from the growth, thyrotropic, or adrenotropic hormones.

media is not well known. It should be noted that the oral administration of any part of the whole gland is without visible effect because it is destroyed by proteolytic enzymes and the hormones are protein in nature, or at least inseparable from proteins.

The Anterior Pituitary

The anterior pituitary exerts at least ten functions. Six of these are due to different hormones. There is some doubt whether the other effects are due to specific hormones. The six known hormones are:

1. The growth-stimulating or somatotropic hormone
2. The thyrotropic hormone
- 3 The adrenotropic hormone



Fig. 37.—A, to show the appearance before the onset of acromegalic symptoms; B, the appearance after seventeen years of the disease. (After Campbell Geddes) (From Bard: *Macleod's Physiology in Modern Medicine*.)

4. and 5. The gonadotropic hormones, male and female
 - a. Follicle-stimulating (gametogenic)
 - b. Luteinizing, causing luteinization of ovarian follicles
 6. Prolactin, or the lactogenic hormone
- Others less definitely established are:
7. Ketogenic
 8. Hyperglycemic, or diabetogenic
 9. Parathyrotropic
 10. Pancreatropic

that pancreatic ferments destroy insulin. Banting and Best focused their attention on the islets, and to avoid the interfering influence of the other parts of the gland, ligated the pancreatic ducts, and also worked with early fetal pancreas. In both cases trypsin production in the gland is markedly reduced or absent, while it is believed that the islets of Langerhans are functioning. Extracts from such pancreas were found to cause a great reduction of blood sugar. Repeated daily injections permitted animals with the pancreas removed to live beyond the span of life usual under such conditions. Later, methods were developed for the extraction of insulin from adult pancreas, and continuous improvement in the method of extraction has been made. Insulin is now prepared from mammalian pancreas (sheep, hogs, cattle). In the earlier experiments, 10 rabbit units were obtained from a kilogram of pancreas. By improved technique, 4000 or more units are now obtained.

Chemistry of Insulin.—The active material in insulin is a protein which upon hydrolysis yields a number of amino acids. In its crystalline state it appears to be chemically linked with certain metals (zinc, nickel, cadmium, or cobalt). Normal pancreatic tissue is rich in zinc, a fact which may be of significance in the natural storage of the hormone. Insulin keeps rather well in a slightly acidified state but is unstable in dilute alkali. Slight changes in its chemical structure greatly changes its behavior and for this reason it cannot be given by mouth.

Physiologic Action.—Since relatively small amounts of insulin are necessary in the body tissues, it is thought that insulin acts as a catalyst in cellular metabolism.

Carbohydrate metabolism is controlled by a finely balanced interaction of a number of endocrine factors (adrenalin, anterior pituitary, thyroid, and insulin), but the particular phase of carbohydrate metabolism which is affected by insulin is not known. When insulin is injected hypodermically, however, it produces a rapid lowering of the blood sugar. This effect is produced in both normal and diabetic patients. Moderate amounts of insulin in the diabetic animal promotes the storage of carbohydrate in the liver and also in the muscle cells, particularly after the feeding of carbohydrate. In the normal animal, there is also an increase in the deposit of muscle glycogen but apparently no increase in the level of liver glycogen.¹ In both the normal and the diabetic individual the oxygen consumption increases and the respiratory quotient rises.

¹Best and Taylor: *The Pharmacological Basis of Medical Practice*, Baltimore, 1945, Williams and Wilkins Co., p. 972.

Hyperglycemic or Insulin Antagonizing Effect.—Insulin in amounts not harmful to a normal dog brings about coma and death in the hypophysectomized animal. In toads, pancreatectomy produces intense diabetes. If the pituitary be removed, no diabetes develops. If, however, the anterior pituitary be implanted beneath the skin, diabetes develops (Houssay).

Preparations.—

There are no official preparations of the anterior pituitary although there are a number on the market.

Anterior Pituitary Extract.—Dosage: 0.5-5 cc. (8-75 minims) intramuscularly. This is said to contain the growth-promoting factor as well as the gonadotropic and thyrotropic factors.

Other gonadotropins are mentioned in the previous chapter.

Posterior Lobe Hormones

Extracts of the posterior lobe are used particularly in obstetrics and for conditions which are relieved by increased intestinal peristalsis. These hormones are discussed in greater detail under the drugs affecting the reproductive system, Chapter XIX, and also in Chapter XIII, page 388.

Insulin

The discovery of insulin begins with Johann Conrad Brunner (1653-1727), the discoverer of Brunner's glands in the duodenum. In 1683 he made incisions in the pancreas of a dog, after which the dog had extreme thirst and polyuria. Brunner suggested that there is a connection between the pancreas and diabetes. This seems to be a pioneer experiment on the internal secretions of the pancreas.

In 1889, von Mering and Minkowski showed that removal of the pancreas from dogs produces symptoms identical with diabetes mellitus. In 1906 Minkowski showed that this experimental diabetes could be prevented by pancreatic grafts. This work practically proved that the pancreas produces an internal secretion or hormone that controls carbohydrate metabolism. Corroborative findings soon followed. Partial removal of the pancreas produces a mild diabetes in animals, and transfusion of normal blood ameliorates the symptoms. In autopsy of diabetic patients, changes in the islets were found. This indicated that the hormone was produced in the islets. Repeated attempts to isolate the hormone failed until Banting and Best in 1921 isolated it in sufficiently pure state to permit its use in diabetic patients. The difficulty in isolating it lay in the fact

tient with schizophrenia. It is a dangerous treatment with a relatively high mortality and should be used only by those who are well equipped, qualified, and familiar with the procedure.

Administration.—Insulin is given hypodermically into the loose connective tissues of the body, usually into the arms or thighs. It cannot be given by mouth because it is destroyed by digestive enzymes. Regular insulin is usually given about twenty minutes before the meal. It is somewhat irritating and since the tissues of the diabetic patient are likely to be less resistant to the invasion of pathogenic organisms than normal tissue, the technic used in administration of insulin should be flawless. The same site of injection should not be used repeatedly, but a plan of rotation should be followed so that the same site is not used oftener than once a month.

There is no average dose of insulin for the diabetic; each patient's needs must be determined individually. Unless complications are present, insulin should not be used if the patient's glucose tolerance is sufficiently high to provide him with a diet sufficient for light work.

Dosage of insulin should be expressed in units rather than in cubic centimeters or minims. Insulin injection is so standardized that each cubic centimeter contains 20, 40, 80, or 100 U. S. P. units per cc. One insulin unit will on the average promote the metabolism of approximately 1.5 Gm. of dextrose.¹ In order to estimate the necessary insulin dosage for the patient the physician must know how much dextrose will be obtained from the diet and what the patient's glucose tolerance is, i.e., how much insulin the patient is able to make for himself. Insulin must be regularly administered and must be accompanied by carefully estimated diets of known composition.

It is important that the symptoms of diabetes be adequately controlled because the more nearly the blood chemistry of the diabetic patient is restored to normal, the more normal his metabolism and nutrition will be and the less degenerative damage will occur in organs like the eye and the heart.

Preparations.—

Insulin Injection (Injectio Insulini), U. S. P.

An acidified aqueous solution of the active principle of the pancreas which affects the metabolism of glucose. This preparation is marketed in 5 cc. and 10 cc. ampules.

¹N. N. R., 1947, p. 361.

Diabetes Mellitus.—Diabetes mellitus is a disease of metabolism characterized particularly by an inability to use carbohydrate. The blood sugar becomes elevated and when it exceeds a certain amount the excess is excreted by the kidney (glycosuria). In diabetes mellitus there is a failure to store glycogen in the liver. This derangement of carbohydrate metabolism results in an abnormally high metabolism of proteins and fats. The normal short-chained fatty acids, which result from oxidation of fatty acids, accumulate faster than the muscle cells can oxidize them, resulting in the development of ketosis and acidosis. The symptoms of diabetic coma and acidosis are directly or indirectly due to the accumulation of acetone, beta-hydroxy-butyric acid, and diacetic acid. Respirations become rapid and deep, the breath has an acetone odor, the blood sugar is elevated, the patient becomes dehydrated, and stupor and coma develop unless treatment is promptly started.

Therapeutic Uses of Insulin.—1. Insulin is a specific in the treatment of diabetic coma and acidosis. The administration of glucose intravenously often accompanies the administration of the insulin. Glucose and insulin promote the formation and retention of glycogen in the liver and the oxidation of fat in the liver is arrested. Therefore the rate of formation of acetone bodies is slowed and the acidosis is checked. Other supportive measures such as the restoration of the fluid balance of the body are exceedingly important.

2: Insulin has its principal use in the control of symptoms of diabetes mellitus when this disease cannot be satisfactorily controlled by a dietetic regime alone. Certain mild cases of the disease can be treated by diet alone, but many patients require insulin in order to live active and useful lives. The dosage must be determined for each individual patient and can be best done when the patient is under the direct observation of the physician for a period of time. A number of factors determine the amount of insulin needed by the patient, and this means that a patient's needs are not always constant. Adjustments in dosage may be necessary if infection is present or if the patient has an anesthetic, or if emotional strain and stress are present or if his amount of activity is increased or decreased.

3. Insulin is sometimes employed in conditions of malnutrition when it is advisable to increase the patient's appetite. The lowering of the blood sugar causes hunger contractions and thus increases the patient's desire for food.

4. Insulin has also been used in psychopathic hospitals for the purpose of producing hypoglycemic shock for its effect on the pa-

to the amount of insulin given. In man toxic symptoms occur when the blood sugar falls below 79 mg. per 100 cc. The point at which the symptoms become noticeable varies greatly, however. For each person there is a level at which very severe symptoms or the convulsive stage of hypoglycemia is reached.

Early symptoms include a feeling of weakness, sweating, nervousness and anxiety, pallor or flushing, and a vague feeling of apprehension. If the patient does not receive treatment, the symptoms may be intensified with the development of aphasia, convulsive seizures, coma and even death. When the first mild symptoms are noted, the patient should receive treatment at once. Prolonged hypoglycemia is associated with diminished oxygen consumption and irreparable injury of the nervous system. Symptoms of hypoglycemia are quickly relieved by the administration of a soluble carbohydrate in the form of orange juice or two or three lumps of sugar by mouth or a soluble carbohydrate intravenously if the patient is comatose. Injections of adrenalin are sometimes used in an emergency, and this is effective because it causes the liver to release more sugar into the blood. This measure should be followed by the administration of carbohydrate.

Ambulatory patients learn to recognize sudden hunger, sweating, and nervousness as subjective signs of insulin overdosage and learn to carry a few lumps of sugar with them. A night nurse may find a diabetic patient asleep but in a pool of perspiration, a fact which would lead her to suspect that he was having an insulin reaction and that he should be awakened and given treatment.

The Adrenal Gland Hormones

The adrenal (suprarenal) glands, which are located just above the kidneys, consist of two parts, the medulla and the cortex. Epinephrine, the secretion of the medullary portion, is discussed in the chapter on Drugs Affecting the Nervous System, page 215. The secretion made by the cells of the cortex is distinctly different from epinephrine. Adrenalectomized animals die within a few days unless they are given injections of adrenal cortex while removal of the medullary portions of the gland does not result in death.

Addison's Disease was first described by Thomas Addison in 1855. The disease is characterized by a bronze pigmentation of the skin, hypotension, asthenia, loss of weight and symptoms of gastrointestinal disturbance. The onset is insidious and there is a progressive development until the patient reaches a point of exhaustion. There is a disturbance of water metabolism brought about by excessive

Protamine Zinc-Insulin Injection, U. S. P.

A preparation of insulin to which has been added an appropriate amount of protamine and a zinc salt. The effects produced by protamine zinc insulin are the same as those of insulin except that the blood sugar-lowering action is much more prolonged. It may be used in place of unmodified insulin or in combination with it. The chief indications for its use are in those cases where the unmodified insulin does not provide control of symptoms unless it is given in several daily doses or in cases where lack of control is evidenced by frequent hypoglycemic reactions, ketosis, or pronounced fluctuations in blood sugar levels. Protamine zinc insulin is usually administered either in the morning one-half to one and one-half hours before breakfast, or in the evening one hour before supper, or before retiring. Its maximum blood sugar-lowering action is about twelve to twenty-four hours after administration.

Hypoglycemic reactions are less easily recognized than with the regular insulin. Sometimes the main symptom is a feeling of pronounced fatigue out of proportion to the degree of activity. Treatment consists of giving a combination of a rapidly absorbed and a slowly absorbed carbohydrate, something like bread and honey. Protamine insulin is of no value in emergencies such as coma. A combination of protamine insulin and rapid-acting insulin is frequently necessary if adequate control of symptoms is to be maintained. It is administered subcutaneously, never intravenously. It should be well mixed (but not made to foam) before withdrawal from container in order to obtain a uniform suspension.

Crystalline Zinc Insulin Injection, N. N. R.

A solution of zinc insulin crystals especially indicated for patients who may be expected to exhibit allergic reactions to insulin. Experience has shown that crystalline zinc insulin injection and insulin may be used interchangeably.¹

The potency of this preparation is measured in terms of the standard units of insulin. The general principles underlying its administration are the same as those for the use of insulin.

Symptoms of Overdosage.—The symptoms of hypoglycemia develop in the patient who is given an overdose of insulin or in the patient with hyperinsulinism due to certain changes in the pancreas. When due to overdose of insulin the fall in blood sugar is in proportion

¹N. N. R., 1947, p. 365.

patients often show further improvement when they are given additional therapy in the form of adrenal cortex preparations.

Uses for Cortical Extracts.—The specific therapeutic use of extracts of the cortex of the adrenal gland, both the natural and the synthetic form, is for patients with Addison's disease in whom the symptoms of the disease cannot be controlled by a diet low in potassium accompanied by adequate quantities of sodium salts.

The use of the synthetic preparation greatly reduces the cost of treatment, and it is relatively stable and of uniform potency which makes exact regulation of dosage easier than when natural extracts of the gland are used. Its administration is usually supplemented with that of sodium chloride, although both must be carefully regulated to prevent the formation of edema and serious circulatory disturbances.

Authorities recommend that patients past middle age be given rather small doses of the extract and that the activity of patients be restricted, particularly during the first few weeks of treatment. Adjustments of dosage of the extract of the synthetic hormone must be made when the patient is subjected to warm weather, infection, or sudden change in the diet.

It is generally conceded that the use of cortical hormone has been very valuable in making it possible for the patient with Addison's disease to live a fairly normal life in a moderately good state of health with relatively few complications or crises. The survival time for these patients has been appreciably increased whereas a few years ago a few months of survival was as much as could be expected in many cases.

Toxicity.—Administration of large amounts of the synthetic adrenal hormone to animals has resulted in atrophy of the adrenal cortex. It is possible that the same effect is obtained in man. When large doses of both the hormone and sodium chloride have been given patients, edema, sudden increase in weight, hypertension, symptoms of congestive heart failure, and even death have resulted. If edema occurs during treatment, the treatment should be stopped and the intake of sodium chloride reduced. Blood pressure should be checked frequently in the course of treatment, and the drug stopped if hypertension occurs. The fact that the synthetic hormone of the adrenal cortex is an extremely potent substance and that it is capable of producing severe reactions explains why the drug has not been accepted by New and Nonofficial Remedies and why its therapeutic status must be substantiated by further investigation and study.

excretion of sodium by the kidney, and also a retention of potassium, a disturbance of carbohydrate metabolism, and a failure to store glycogen normally.

The patient usually has marked nausea and vomiting and diarrhea; he becomes greatly dehydrated and generally incapacitated when the disease is present in a severe form. It has been shown that the condition is due to an adrenal cortex insufficiency. Diagnosis is often difficult because numerous other conditions may give rise to one or more of these symptoms.

Chemistry and Function of Adrenal Extracts.—Extracts of the adrenal cortex contain a number of substances which influence electrolyte, carbohydrate, and water metabolism.¹ No one substance has been found which possesses all of the effects of cortical extract. A number of crystalline compounds have been isolated from the cortex and have been found to be steroids, the most potent of which are *corticosterone* and *dehydrocorticosterone*. These, as well as the other chemically related substances of the adrenal cortex, resemble the sex hormones, particularly the androgens. Desoxycorticosterone, a related substance, has been prepared synthetically and is available as desoxycorticosterone acetate. It has been found to be concerned chiefly with salt and water metabolism, but its use does not represent full replacement therapy.² It is capable of maintaining life in the adrenalectomized animal, but it is not capable of all of the functions of the adrenal cortex and is particularly lacking in the ability to regulate carbohydrate metabolism.

Physiologic Action of the Cortical Hormones.—When cortical extracts are administered to the patient with Addison's disease, the concentration of serum sodium increases and this leads to an increase in blood volume and a corresponding rise in blood pressure. The serum potassium falls, renal function improves, and body weight and muscular strength increase. Pigmentation is not appreciably affected. The chief site of action is thought to be on the renal tubule where it restores the ability of the cells to reabsorb sodium and reject potassium.³

When crystalline desoxycorticosterone is injected, it is capable of maintaining life since it is particularly effective in correcting defects in the sodium-potassium balance but it has been noted that

¹N. N. R., 1947, p. 335.

²Hampton, H. Phillip, and Kenler, E. J.: Addison's Disease: Treatment and Prognosis. Collected Papers of the Mayo Clinic and Mayo Foundation, 1941, p. 427.

³Goodman and Gilman, p. 1238.

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Authorities recommend that patients past middle age be given rather small doses of the extract and that the activity of patients be restricted, particularly during the first few weeks of treatment. Adjustments of dosage of the extract of the synthetic hormone must be made when the patient is subjected to warm weather, infection, or sudden change in the diet.

It is generally conceded that the use of cortical hormone has been very valuable in making it possible for the patient with Addison's disease to live a fairly normal life in a moderately good state of health with relatively few complications or crises. The survival time for these patients has been appreciably increased whereas a few years ago a few months of survival was as much as could be expected in many cases.

Toxicity.—Administration of large amounts of the synthetic adrenal hormone to animals has resulted in atrophy of the adrenal cortex. It is possible that the same effect is obtained in man. When large doses of both the hormone and sodium chloride have been given patients, edema, sudden increase in weight, hypertension, symptoms of congestive heart failure, and even death have resulted. If edema occurs during treatment, the treatment should be stopped and the intake of sodium chloride reduced. Blood pressure should be checked frequently in the course of treatment, and the drug stopped if hypertension occurs. The fact that the synthetic hormone of the adrenal cortex is an extremely potent substance and that it is capable of producing severe reactions explains why the drug has not been accepted by New and Nonofficial Remedies and why its therapeutic status must be substantiated by further investigation and study.

Administration.—Desoxycorticosterone acetate is usually injected intramuscularly in oil. It can be absorbed from the gastrointestinal tract but some of its activity is lost that way.

The implantation of pellets subcutaneously has been advocated for patients who have been successfully treated for a period of time. However the formation of scar tissue at the site of implantation has made this form of administration somewhat unpopular. Another method of administration which provides for gradual liberation of the hormone is a mixture of the hormone and beeswax which is injected into the subscapular region.

Adrenal cortex extracts are active by mouth but cannot be relied upon in a crisis. They are usually given parenterally.

Preparations.—

There are a number of cortex preparations on the market which are dependable, but only one has been accepted for inclusion in N. N. R.

Adrenal Cortex Extract, N. N. R. (Upjohn). An extract of adrenal gland. Available in 10 cc. vials. Each cubic centimeter contains not less than 50 dog units of cortical activity. Dosage varies widely and is dependent upon the degree of cortical insufficiency, the general condition of the patient, and the presence of complications. Dosage varies from 100 to 500 dog units daily to 2500 to 5000 dog units for the patient in crisis.¹

Eschatin (Parke, Davis and Co.). A purified extract of whole adrenal cortex. Available in vials of 10 cc. and 50 cc. Each cubic centimeter contains the equivalent of 40 grams of fresh gland or 10 dog units per cc.

Desoxycorticosterone Acetate, U. S. P.—A synthetic component of adrenal cortex which may be administered intramuscularly or by implantation. The dosage must be determined in accordance with patient's needs. It is marketed in the form of solutions in sterile peanut or sesame oil under the names of *Doca* (Roche-Organon), *Cortate* (Schering), and *Percorten* (Ciba).

Questions for Review

1. Discuss the use of calcium in therapeutics.
2. List some of the preparations of calcium which you have given or seen given to patients in your hospital and indicate conditions for which these preparations were given.
3. Give the action, uses and dosage of phosphorus.
4. Give the preparations, uses and dosage of iodine.
5. Give the action, dosage and method of administration of cod-liver oil.

¹N. N. R., 1947, p. 337.

6. What is the chief use of viosterol? Of yeast?
7. Explain why patients suffering from hyperthyroidism may be given several doses of Lugol's solution daily.
8. What is the meaning of the word *vitamin* and how did the name originate?
9. What constitutes an adequate diet from which no normal adult would develop an avitaminosis?
10. Which vitamin or vitamin complex is particularly essential for normal function of the nervous, circulatory, and digestive systems?
11. Make a list of the number of patients on your ward who are getting vitamin concentrates. Indicate the condition for which they are given and the results observable.
12. The following conditions would suggest a lack of what vitamins in the diet?

Rickets	-----
Scurvy	-----
Polyneuritis	-----
Pellagra	-----
Prolonged clotting time of the blood	-----
13. What vitamin preparation has been known to have harmful body effects when fed in excessive amounts?
14. What is meant by hormone therapy?
15. Discuss the danger involved in the commercialization of vitamin and hormone preparations as they are made known to the public.
16. Discuss good and poor advertising methods as they relate to medicinal preparations. Why does conservatism tend to characterize the medical circles of high repute?

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UNIT XIII

CHAPTER XXII

SERUMS AND VACCINES

Serum Therapy

Serum therapy is based upon the phenomena known as immunity, or the resistance of the body to the invasion of pathogenic bacteria. It is a specific therapy.

Immunity is of two kinds, natural and acquired. If an individual is so constituted that the germ of a disease will not grow upon his tissues, or that the toxins of that germ are harmless to him, he is immune to that particular disease. Such immunity is called *natural immunity*.

When natural immunity is not effective and bacteria attack the tissues and live and grow at their expense, the body protects itself by preparing substances destructive to the particular organism making the attack. These substances are called "antibodies." They are present in the blood and other body fluids and are carried to the point of infection by the blood and lymph. The antibodies gradually disappear from the blood, but the body cells have seemingly acquired the ability to resist the same bacteria when they attack the tissues again. Immunity due to these antibodies, as well as the special ability to produce them, is known as *acquired immunity*; and because the individual himself developed the antibodies, the immunity is known as *active immunity*. It is usually present after an attack of an infectious disease such as smallpox, typhoid fever, etc., and may be induced artificially by the injection of substances known as antigens. The antigen may be a virus, that is, a suspension of living microorganisms, as, for example, the smallpox virus; or a vaccine, a suspension of dead microorganisms, as typhoid vaccine; or it may be an extract of the bodies of bacteria, as tuberculin; or a soluble toxin produced by bacteria, of which diphtheria toxin is an example.

Passive acquired immunity against certain diseases is secured by transferring to a person the blood serum of an animal which has been actively immunized by injections with the specific organisms of those diseases. Immunity acquired in this way is called *passive immunity* because the body plays no part in the preparation of the antibodies.

The body cells are not educated to resist infection as they are in active immunity, and as the blood is renewed, the antibodies are lost, and the patient is in the same condition as if no serum had been administered.

SERUMS

An immune serum is the serum of an animal which has been injected with the dead or live cultures or with the toxin of a specific bacterium with the result that protective or immune bodies have been formed and circulate in the blood stream.

Serum treatment consists in the transfer of the immune serum into the circulation of the patient. This immune serum contains specific antibodies which act upon disease germs.

There are several kinds of curative serums: the naturally produced, the bacteriolytic or antibacterial, and the antitoxic.

These biologic preparations are potent and even dangerous. Export or interstate sale, the tests for potency, the preservatives which may be used, and the expiration date on which they may be used are regulated by the United State Government. It is quite important that they be purchased from reputable and dependable manufacturers.

Naturally Produced Serums

These are preparations obtained from normal blood, such as plasma, serum or globulins or serum from patients who have recovered from a disease and retain the immune bodies in their blood serum.

Human Immune Globulin (*Globulinum Immune Humanum*), U. S. P. (Measles Prophylactic, Placental Extract).—This is a preparation of globulin obtained from human placental blood which contains antibodies against measles.

It is useful in the prevention of measles as well as in the treatment of that disease. It is thought to be as useful as convalescent serum and is more readily available.

The dosage varies with a number of factors. For modification of measles 2-5 cc. (30-75 minims); for prevention 2-10 cc. (30-150 minims) intramuscularly.

Human Measles Immune Serum (*Serum Immune Morbilli Humanum*), N. F.—Human measles serum is sterile blood serum obtained from the blood of a healthy human being who has recovered from an attack of the measles. This serum complies with the requirements of the National Institute of Health of the United States Public Health Service.

Dosage: Therapeutic—20 cc. parenterally.

Prophylactic—10 cc. parenterally.

Human Scarlet Fever Immune Serum (Serum Immune *Scarlatinae Humanum*), N. F.—Human scarlet fever immune serum is the sterile serum obtained from the blood of a healthy human being who has survived from an attack of scarlet fever. It complies with the requirements of the National Institute of Health of the United States Public Health Service.

Dosage: Prophylactic—10 cc. parenterally.

Therapeutic 20 cc. parenterally.

Bacteriolytic Serums

A bacteriolytic serum is the serum of an animal which has been injected with a solution of the particular bacteria against which protection is desired. The serum contains antibodies which, when injected into a person suffering from the disease, attack the bacteria directly, and destroy them. The antitoxic serum neutralizes the toxin.

PREPARATIONS

Antianthrax Serum, N. N. R.—The serum of a horse which has been immunized against the anthrax bacillus. By its use, an infection which hitherto has proved fatal in a great many cases can now be controlled, if it is recognized early enough. In mild cases with a small lesion, 50 cc. of the serum are given every 12 or 24 hours. The first injection should be made intravenously, the subsequent ones intramuscularly or subcutaneously. In more severe cases, in which the general symptoms are pronounced, 50 to 100 cc. should be given intravenously every 8 to 12 hours for 3 or 4 doses, then intramuscularly. In very severe cases, 200 to 300 cc. should be given every 3 to 6 hours until signs of septicemia disappear. The serum should be warmed before injection and given very slowly. Locally 10 to 12 cc. should be injected into the edge of the lesion itself and into the tissues underlying the pustule.

Antidysenteric Serum, N. N. R.—The serum of a horse which has been immunized against the Shiga bacillus. It has no effect in amebic dysentery. In mild conditions, the serum is used hypodermically in doses of 20 cc. for an adult and about 10 cc. for a child. If the infection is severe, it may be given intravenously and in adult doses as large as 50 to 100 cc. Improvement in the patient's condition is usually prompt, the nervous symptoms diminishing in a few hours and the diarrhea within 24 hours. Complete recovery may

take place in less than a week if treatment is started early in the course of the disease. Antidysenteric serum may also be used in 5 cc. doses as a prophylactic, but protection lasts only about two weeks. Probably chemotherapeutic preparations should take preference over this serum in routine treatment.

Antimeningococcic Serum (Serum Antimeningococcicum), N. F.—The serum of a horse immunized with cultures of the several types of meningococci (*Neisseria intracellularis*) which prevail in the United States. If used early enough in the infection, the serum reduces the mortality of epidemic cerebrospinal meningitis approximately 60 per cent. It causes the turbid spinal fluid to become clear and facilitates phagocytosis and arrests the growth of specific microorganisms as well. Its effects are bactericidal as well as antitoxic. It not only saves life but greatly decreases the frequency with which those patients who recover from attacks suffer from sequelae, such as deafness, blindness, and deformities.

Antimeningitis serum is usually given by intraspinal injection. However, if the coccus is found in the blood, the serum may be given intravenously in doses of about 100 cc. to facilitate phagocytosis. Average therapeutic dose 20 cc

Antipneumococcic Serum (Serum Antipneumococcicum), N. F.—Antipneumococcic serum is obtained from the blood of an animal which has been immunized with cultures of a pneumococcus of one of the types for which a serum has been prepared and which has been standardized or is released by the National Institute of Health of the U. S. Public Health Service

Type specific antipneumococcic serums are useful in the treatment of pneumococcic pneumonias and their use has largely replaced the practice of administering combined serum of more than one of the common types. Some 38 types and 12 additional subtypes of pneumococci have now been recognized.

It is thought advisable not to neglect other therapeutic measures of treatment such as chemotherapy. The antipneumococcic serum from rabbits has certain advantages over that obtained from horses. It is thought that the rabbit serum penetrates infected tissues more readily

The average therapeutic dose by parenteral injection is from 20,000 to 100,000 units. It is advisable to give 10,000 units for the first dose, followed in one hour by a dose of 20,000 units. The second dose may be repeated at intervals of four to six hours until the temperature falls and beneficial effects are evident.

Antitoxic Serums and Antitoxins

The antibodies are formed in the blood of the larger domestic animals which have been actively immunized by a specific antigen. The animal is then bled and the serum separated from the blood. It is then purified in most instances to remove inactive substances and to concentrate the antibodies. Antitoxins, which are a useful class of antibodies, are given to neutralize the toxins produced in certain diseases.

Diphtheria Antitoxin (*Antitoxicum Diphthericum*), U.S.P.—Diphtheria antitoxin is prepared most satisfactorily by injecting healthy horses hypodermically at four-day intervals with diphtheria toxin. The toxin, prepared by growing diphtheria on broth cultures, is sterilized before being injected into the horse. The living bacilli are not injected, and the horse does not become infected with diphtheria, but acquires a tolerance. By increasing the dose injected, a high antitoxin power of the serum is reached in from four to six months. The animal is then bled from the jugular vein, which can be accomplished easily without an anesthetic, and from 6 to 12 liters of blood may be collected in sterile containers.

After the serum or plasma from the immunized animal has been collected, the antitoxin-bearing globulins are separated from the other constituents of the serum or plasma and dissolved in water. Sodium chloride and a preservative are then added and the solution is filtered through a bacteria-excluding filter. It has a potency of not less than 500 antitoxic units per cubic centimeter.

The unit of diphtheria antitoxin is the amount of antitoxin which, when mixed with an L (plus) dose of toxin and injected subcutaneously into a guinea pig weighing 250 grams, will preserve the life of the guinea pig for four or five days only.

An L (plus) dose of toxin is the quantity of toxin that will neutralize one antitoxin unit, and, in addition, kill a 250-gram guinea pig in four or five days.

In commercial practice, where a margin of safety is advantageous, the unit of diphtheria antitoxin is considered to be that amount of the antitoxin which will save the life of a guinea pig if injected together with an L (plus) dose of toxin.

Therapeutics.—Diphtheria antitoxin is used as a prophylactic and also as a curative agent.

Passive Immunization.—A dose of 500 units for infants under one year and 1000 units for older children will confer immunity for from two to four weeks. This is sometimes used in cases of children who

have been known to be exposed closely to diphtheria. If the conditions will permit, the Schick test should first be made and only those persons who give positive reactions need be immunized.

Active Immunization.—It has been found that a mixture of strong diphtheria toxin which has been neutralized by the addition of antitoxin (T.A.), or in which the toxin is in very slight excess (as has been shown by injection into a guinea pig), when given subcutaneously at weekly intervals, in doses of $\frac{1}{2}$ cc. for infants under one year and 1 cc. for older children and adults, confers active immunity which lasts for three years or longer. One injection is said to give immunity in 80 per cent of susceptible cases, 2 injections in 90 per cent, and 3 injections in 97 per cent of cases. Park found no serious trouble in 10,000 cases.

The serum treatment of diphtheria has reduced the mortality of the disease at least two-thirds. The chances of recovery in all cases vary directly with the time of administration. Poulsson reports 857 cases from the hospital in Oslo treated with antitoxin, with the following results:

Those who received the serum on the first day of the

disease	-----	there were no fatalities
Those on the second day	-----	1½ per cent fatalities
Those on the third day	-----	6 per cent fatalities
Those on the fourth day	-----	8 per cent fatalities
Those on the fifth day	-----	14 per cent fatalities
Those on the sixth day	-----	21 per cent fatalities

The reason for these striking differences is explained by the fact that when the toxin has time to unite with the cells of the body, it has done much injury and cannot unite with the antitoxin. If, however, the antitoxin is in the blood when the toxin is liberated, it quickly neutralizes it.

It has also been found that laryngeal and other forms of diphtheria are influenced in the same way as faucial infection. Where tracheotomy is necessary, the antitoxin lessens the likelihood of growth of diphtheria in the wounds.

Dosage.—In case of faucial or tonsillar diphtheria of moderate severity, the initial dose should be not less than 5,000 units on the first day of the disease, 10,000 units if seen first on the second day of the disease, and 20,000 if seen later. If this does not cause a fall in the patient's temperature and an improvement within twelve to twenty-four hours, the injection should be repeated. The dose for

children under two years should be about one-half of that given above. In very severe cases the danger lies more in using too little than too much.

Administration.—Antitoxin should be given subcutaneously or intramuscularly, except in malignant or profoundly toxic cases, when it may be given intravenously. Injections should be made under aseptic precautions, and after injection the part may be massaged to hasten absorption. The dose for intravenous injection should be $\frac{1}{2}$ to $\frac{2}{3}$ that of the subcutaneous dose, and it should be injected slowly and at body temperature.

If there is reason to suspect hypersensitivity to horse serum, a test dose of 0.05 cc. of a 1:10 dilution of the serum should be injected subcutaneously. This may be repeated several times at fifteen-minute intervals; if there is no reaction, a full dose may be injected.

Untoward Effects.—Serum sickness occurs in a small percentage of cases. Anaphylactic shock may also occur, but it is rare. According to Park, one death has occurred in about 70,000 persons from injecting with serum.

The symptoms of serum sickness usually appear about a week after the injection of serum. They vary in character, but the chief symptoms are cutaneous eruptions, fever, and painful joints. Rapid relief may be obtained by the administration of epinephrine.

Bivalent Gas Gangrene Antitoxin, U. S. P.—An antitoxic serum prepared by immunizing horses with the toxins of *Clostridium perfringens* (*welchii*) and *Clostridium septicum* (*Vibrio septique*). The antitoxic antiserum is prepared in a manner similar to that used for the other antitoxic serums. Potency is determined according to the methods described by the National Institute of Health of the United States Public Health Service.

Dosage: 10,000 to 40,000 units intramuscularly or intravenously, preferably the latter. Dose repeated every twelve to twenty-four hours, depending on the condition of the patient.

Pentavalent Gas Gangrene Antitoxin, U. S. P., is a sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of the following organisms: *Clostridium perfringens*, *Clostridium septicum*, *Clostridium aedematiens*, *Clostridium bifermentans*, and *Clostridium histolyticum*.

It complies with the requirements of the National Institute of Health of the United States Public Health Service.

Average dose: Parenteral, therapeutic, or prophylactic, the contents of one or more packages as the initial dose.

Trivalent Gas Gangrene Antitoxin, U. S. P., is a sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of *Clostridium perfringens*, *Clostridium septicum*, and *Clostridium oedematiens*.

Average dose Parenteral, therapeutic, or prophylactic, the contents of one or more packages as the initial dose.

Scarlet Fever Streptococcus Antitoxin (Antitoxinum Scarlatinae Streptococcicum), U. S. P.—Scarlet Fever Antitoxin, is prepared in a manner similar to that given for diphtheria antitoxin. It has a potency of not less than 400 antitoxic units per cubic centimeter. Average dose: by parenteral injection, therapeutic, 6000 units; prophylactic, 2000 units.

The federal unit for scarlet fever antitoxin was adopted in 1929 and is the smallest amount of antitoxin which neutralizes 50 skin-test doses of scarlatinal streptococcus toxin. The skin-test dose is the least quantity of toxin, which, injected subcutaneously into persons known to be susceptible to the toxin, will induce a reaction equal to that induced on the same persons at the same time by the injection of a skin-test dose of the standard toxin supplied by the U. S. National Health Institute. This dose is contained in 0.1 cc. The reaction is observed twenty-four hours after the injection of the toxin, and is considered positive if a red area develops, measuring at least 1 centimeter in diameter. (Bayne Jones.)

This antitoxin is marketed in syringes containing the amount to be injected weekly or one therapeutic or prophylactic dose. The prophylactic dose is not so extensively employed because the passive immunity conferred is so brief and because of the danger of anaphylactoid shock should it be necessary to give a therapeutic dose soon afterward. After a prophylactic dose, immunity should be established in a few weeks, as shown by the Dick test.

Tetanus Antitoxin (Antitoxinum Tetanicum), U. S. P.—This antitoxin is prepared from the horse in much the same way as diphtheritic antitoxin, but the animal in this case has been immunized against tetanus toxin. Each cubic centimeter, U. S. P., contains not less than 400 antitoxic units.

Tetanus Antitoxin must comply with the requirements of the National Institute of Health of the United States Public Health Service.

Tetanus Antitoxin must be dispensed in the unopened glass containers in which it was placed by the manufacturing establishment,

and it should be preserved at a temperature between 2° and 10° C., preferably at the lower limit.

Average Dose: Curative, 20,000 units. Protective 1,500 units.

Tetanus and Gas Gangrene Antitoxins, U. S. P.—An antitoxin made by mixing the serums of horses individually immunized to the toxins of tetanus and gas gangrene. Each package of the antitoxins contains not less than 1,500 units of tetanus antitoxin and not less than 2,000 units of each of the other component antitoxins (*Clostridium perfringens* and *Clostridium septicum*).

VACCINES

The principle of vaccine therapy is to produce active immunity to a disease by infecting the person with the disease in an attenuated form. Vaccination against smallpox is the outstanding example of preventive vaccine therapy. The Pasteur treatment of rabies is an example of curative vaccine treatment. The greatest success with vaccination has been obtained against ultramicroscopic organisms. Some success has also been obtained against certain diseases produced by bacteria. Bacterial vaccines, or bacterins, are sterile suspensions of bacteria in physiological salt solution. Antityphoid vaccination is the best known example in this field. This vaccine is prepared by growing typhoid and paratyphoid bacilli in broth and killing them by heat. Two or three doses are given at an interval of seven to ten days. The second and third doses should be twice the original dose.

Vaccines are preparations prepared in a manner similar to smallpox vaccine. The name comes from the Latin *vaccina* < *vacca*, a cow. Bacterial vaccines are sterilized suspensions of dead bacteria in physiological salt solution or other suitable vehicle. Vaccines do not afford immediate protection. An interval of days or several weeks elapses between inoculation and the production of antibodies. Because of this, if there is danger of immediate infection and there is a serum available, a prophylactic dose of serum should first be given to afford immediate protection, followed later by the vaccine injection to insure a prolonged immunity.

Smallpox Vaccine, U. S. P., was the first vaccine prepared. It consists of a glycerinated suspension of vaccinia vesicles which have been obtained from healthy vaccinated animals of the bovine species. Its preparation and preservation must conform to Federal regulations. It loses its potency if kept at a temperature above 5° C.

Failure of vaccination to take is often due to inactive virus. Vaccine virus contains living organisms that have been attenuated by drying or other means.

Typhoid and Paratyphoid Vaccine, U. S. P. This vaccine is a suspension of the killed typhoid bacilli and the paratyphoid A and B bacilli in suspension in physiologic saline. A cubic centimeter of the vaccine contains at least 1,000,000,000 typhoid organisms and at least 500,000,000 each of the paratyphoid organisms.

The dose given hypodermically is 0.5 cc. and 1 cc.; the latter dose to be repeated once. The interval between doses should be seven to ten days.

By the use of the mixed vaccine, typhoid and paratyphoid infections may be entirely prevented. Within twelve hours a local reaction develops, and usually there are slight fever and a general lack of energy which last about a day. The patient should avoid activity as much as possible during that period.

Immunity lasts from two to four years.

Typhoid Vaccine (Vaccinum Typhosum), U. S. P., is a sterile suspension of killed typhoid bacilli in physiologic saline or other suitable diluent. The vaccine should contain in each cubic centimeter at least 1,000,000,000 typhoid organisms. The average prophylactic subcutaneous dose is 0.5 cc. and 1 cc., the latter dose to be repeated once. The interval between doses should be seven to ten days.

Typhoid vaccine is also used in nonspecific protein therapy.

Epidemic Typhus Vaccine, U. S. P., is a sterile suspension of the killed rickettsial organism of a strain or strains of epidemic typhus rickettsiae.

Average dose: Hypodermic, for active immunization, 1 cc. to be repeated once or twice with seven- to ten-day intervals.

Rabies Vaccine, U. S. P. Rabies vaccine is an attenuated, diluted, dried or dead, fixed virus of rabies. The virus is contained in the dead tissue of the nervous system, especially the cord, of an animal suffering from, or dead of, fixed virus rabies (hydrophobia) infection. The virulence of the toxin is diminished by drying. Immunity to the disease can be produced by injections of emulsions of the cord containing the infective agent, beginning with a minute dose of relatively nonvirulent material and gradually increasing the dose and the virulence of the injected material. The process by which immunity is established is analogous to smallpox vaccination. A modified form of the disease is produced by small quantities of the virus, whose virulence has been lessened by drying. The

treatment sometimes fails and may be followed by untoward symptoms, such as paralysis, which, though usually temporary, may be fatal. Treatment of rabies should be in an institution.

Staphylococcus Vaccine, N. N. R.—A vaccine made from the *Staphylococcus pyogenes aureus*, the *Staphylococcus pyogenes albus*, the *Staphylococcus pyogenes citreus*, or from a mixture of the three. Infections due to these organisms such as carbuncles, furunculosis, and certain types of acne are the ones which respond best to vaccine treatment. An autogenous vaccine, that is, a solution of bacteria obtained from the patient, should be used whenever possible.

Pertussis Vaccine (Whooping Cough Vaccine), N. N. R. A sterile suspension of killed pertussis bacilli. Field studies show that pertussis vaccine possesses sufficient antigenic value to afford considerable protective value against whooping cough. The most satisfactory dose has not been adequately established. It is suggested that the dosage recommended by the manufacturer be followed.*

IMMUNITY TESTS

Diagnostic Diphtheria Toxin, U. S. P. Toxin for the Schick test which is done to determine the susceptibility of an individual to diphtheria. The toxin which is used is carefully standardized on human beings and then diluted so that 0.1 or 0.2 cc, as indicated on the label, will contain the test dose. This is injected into the skin, usually of the forearm. If the person is susceptible to diphtheria, that is, if his blood does not contain a sufficient amount of antitoxin to protect him from the disease, a small area of redness usually with some infiltration will occur at the point of injection in from 24 to 28 hours. This is known as a positive reaction. It persists about a week or ten days and then fades slowly.

Scarlet Fever Streptococcus Toxin, U. S. P. (Dick Test).—A test to determine susceptibility to scarlet fever infection. The scarlet fever streptococcus toxin is so standardized and diluted that 0.1 cc. of the solution contains the test dose. This is injected intracutaneously on the forearm, and in about 24 hours a local reaction occurs which indicates to what degree the patient is susceptible. If the area of reddening is about half an inch in diameter, it is regarded as a positive reaction, while a smaller area is considered negative. Reactions which fade completely within 24 hours are regarded as negative. Positive reactions fade rapidly, and disappear usually within from 48 to 72 hours.

*N. N. R., 1947, p. 457.

Toxins for Immunity

Scarlet Fever Streptococcus Toxin for Immunity.—When there is no history of exposure to scarlet fever, active immunization by means of scarlet fever streptococcus toxin is preferable as it gives more lasting protection. For this purpose subcutaneous injections are given to Dick-positive patients at intervals of 5 or 6 days for 4 doses, each dose being twice as great in strength as the one preceding. The amount of toxin necessary to produce immunity varies with the person. The doses are put up in vials containing the graded strengths. The first dose equals an amount of toxin 250 times as great as that required to produce a Dick reaction; the second dose, an amount 500 times as great; the third, 1000 times as great; and the fourth, 2000 times the amount of the Dick test. The bulk of each injection is 1 cc. Two weeks after the last injection, the skin test should be given to determine whether immunity has been established. The smaller prophylactic doses may cause fever, malaise and sometimes pain in the joints. Large doses induce all the symptoms of scarlet fever toxemia and will not give permanent immunity until such symptoms develop.

Diphtheria Toxin-Antitoxin Mixture, N. N. R.—A fluid containing the toxin of diphtheria, the antitoxin in sufficient amount partially to neutralize the toxin. The mixture establishes a more lasting immunity against diphtheria than the antitoxin alone, but requires a considerable time to produce its effects and therefore is not suitable in an emergency, such as an outbreak of the disease among school children. Under such conditions, Schick-positive children and adults should be given an immunizing dose of antitoxin alone. It is employed chiefly for those who react severely to toxoid, principally older children and adults.* For this purpose, subcutaneous doses of 1 cc. of the toxin-antitoxin are given at intervals of seven days for three doses. Very young children may receive 0.5 cc. for the first dose, and 1 cc. each for the second and third.

Diphtheria Toxoid, U. S. P., an aqueous solution of the products of the growth of *Corynebacterium diphtheriae* so modified by special treatment that it has lost its toxic effects for guinea pigs but not its power to produce immunity. It is administered subcutaneously to produce active immunity in two or three doses with three- or four-week intervals between doses.

Diphtheria Toxoid, Alum Precipitated, U. S. P.—More than 50 per cent of the proteins contained in the original crude toxoid are

*N. N. R., 1947, p. 448.

removed by a purification process. It is administered subcutaneously for active immunization in one or two doses. Because of the presence of potassium aluminum sulfate absorption is delayed. For active immunization it is given subcutaneously in doses 0.5 to 1 cc. and repeated in four to six weeks.

Tetanus Toxoid, Alum Precipitated, U. S. P.—A preparation of tetanus toxin which has been detoxified by the use of formaldehyde with no loss of antigenic properties. The proteins which cause reaction are removed with the use of alum. Tetanus is recommended for active immunization against tetanus, especially for people whose occupation subjects them to greater hazard than usual into becoming infected with tetanus organisms. The dose is $\frac{1}{2}$ to 1 cc. subcutaneously in two doses three months apart.

Tuberculins

Tuberculins are solutions of substances obtained from the tubercle bacillus which are used for the diagnosis and treatment of tuberculosis.

Old Tuberculin, U. S. P. (Koch's Tuberculin), is prepared by filtering a glycerin bouillon culture of the tubercle bacillus through a Berkefeld filter. It contains the toxins of the tubercle bacilli and is used largely in diagnosing tuberculosis. It may be applied locally to a scratch in the skin or injected hypodermically. If the patient is tuberculous, there is an area of redness, usually with a papule at the point of application of the tuberculin, and following hypodermic injection there is a general reaction including a rise in temperature and malaise and an increase in activity at the site of infection. The initial dose for an adult is 0.0002 cc. If there is no reaction, 0.001 cc. and then 0.005 cc. may be tried at intervals of three days.

A reaction indicates that the patient has at some time been infected with tuberculosis but not necessarily that he has clinical tuberculosis.

For treatment 0.00000001 to 0.00001 cc. is the initial dose, and not more than two doses a week should be given.

New Tuberculin.—This is a suspension of pulverized tubercle bacilli in glycerin and water. It is occasionally used in the treatment of tuberculosis.

Snake Bites

Antirabic vaccine for treatment of bites from dogs and other animals has been described.

Poisonous snakes possess hollow teeth or fangs which connect with venom glands situated on the sides of the head. Among the most dangerous reptiles are rattlesnakes, copperheads and moccasins. Fol-

lowing a snake bite, a tight bandage or tourniquet should be placed above the bite to prevent spread of the toxin. The area which is bitten should be promptly cut open with a sharp knife to a depth of about one-fourth of an inch, and suction should be applied to the area from one to two hours, in order to remove the poisonous venom. The tourniquet should be loosened at 20-minute intervals, in order to allow proper circulation to the affected part. Following active suction of the snake bite, tincture of iodine may be applied to the wound. Always call a physician immediately. A product known as Antivenin, N. N. R., is now available in this country; it is curative for rattlesnake, copperhead and moccasin bites, if promptly administered.

N. N. R. describes these venoms as follows:

"CROTALUS ANTITOXIN.—An antitoxic serum prepared by immunizing animals against the venom of snakes of the crotalus family [which includes the rattlesnake, copperhead, and moccasin].

"Action and Uses.—Test on animals show that the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. Crotalus antitoxin is used to neutralize the venom injected by the bite inflicted by members of the crotalus family.

"Dosage.—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously. Recent observations seem to show that there is great advantage in giving the serum in the vicinity of the bite. Use of the antitoxin never should be allowed to replace first aid measures, especially local incision and suction. Perhaps 50 cc. of serum is as small an amount as is likely to prove beneficial.

"Mulford Biological Laboratories, Sharp & Dohme, Philadelphia and Baltimore.

"*Crotalus Antitoxin*—Antivenom Anti-Snake-Bite Serum—
 "Marketed in syringes of 10 cc. (a single dose)."

"BOTHROPS ANTITOXIN.—An antitoxic serum prepared by immunizing animals against the venom of the tropical American serpents of the genus *Bothrops*.

"Actions and Uses.—In animal tests the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. Bothrops antitoxin is used to neutralize the venom injected by the bite inflicted by members of the genus *Bothrops*.

"Dosage.—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously.

"Mulford Biological Laboratories, Sharp & Dohme, Philadelphia and Baltimore.

"Antivenin (Bothropic).—*Tropical American Anti-Snake-Bite Serum.*—An antitoxic serum prepared by injecting horses with venom from serpents of the genus *Bothrops*, especially of the 'Fer-de-Lance' (*Bothrops atrox*). It is claimed to have neutralizing effect against the venom of the genus represented. The venom is extracted and promptly desiccated. It is injected subcutaneously into horses until immunity has been established. The plasma is concentrated by a salting process. Tests on pigeons, the maximum amount of being taken as the titer of the product; mg of the venom when tested on pigeons.

"Marketed in syringes of 10 cc. (a single dose)."

Insect Bites and Stings

For insect bites, the general rule is: soothe, but do not scratch. Scratching a bite seldom brings real relief, and serious infection may follow. Following a mosquito bite, a wet cloth soaked in a solution of baking soda, which is mildly alkaline, will do more to relieve the itching than any amount of rubbing.

The treatment depends on the insect which did the stinging. First, remove the stinger from the wound. Bees leave their stingers like bayonets sheathed in the flesh of their victims. It is best to lift the stinger out of the flesh with the tip of a penknife, rather than to pull it out with the finger. The latter method will squeeze more poison into the wound from the poison sacks, which are still adhering to the stinger. The poison of a bee sting is acid and should be counteracted with an alkaline solution of baking soda or dilute ammonia as is done with a mosquito bite. If the insect which did the stinging was a wasp or hornet, the poison is alkaline and should be treated with an acid solution such as vinegar or lemon juice.

Black Widow Spider

A great deal has been written about the danger of being bitten by the black widow spider. Bogen describes the insect as follows: "*Lactrodectus mactans* is a shiny, coal-black spider usually brilliantly marked with red or yellow or both. The female, which is responsible for the poisonous bites reported, is often one-half inch in length when fully grown, and may stretch its slim glossy black legs over as much as two inches. The markings vary somewhat, the most constant being a bright red patch, shaped somewhat like an hour-glass, on the ventral surface of the abdomen."

A physician should be called immediately in case of a bite by a black widow spider. The bite is followed by severe pain at the

point of the bite, which very quickly becomes generalized. Cramping and spasmodic contractions of the large muscles occur. The patient is prostrated and breathes with difficulty. The abdominal pain may be so severe that acute appendicitis is simulated. In spite of the severe illness, chances of recovery are good. The most important factors in treatment are prompt relief of pain, and magnesium sulfate solution intravenously.

In addition, *Antivenin* (*Latrodectus Mactans*), N. N. R., an antitoxic serum prepared by immunizing horses against the venom of the black widow spider, may be given.

Dosage. 2.5 cc. intramuscularly after proper tests for individual sensitivity.

Allergens

Allergy is a condition of hypersensitiveness to certain proteins, such as the pollens of plants, the proteins present in the hair or skin of animals or the feathers of fowls, and the proteins of food, serums, bacteria, etc. Contact of the person with the proteins to which he is unusually sensitive develops such symptoms as sneezing, coryza, headache, fever, hives and asthmatic attacks.

The principal diseases which result from hypersensitiveness to proteins are hay fever, traceable to the pollens of timothy, ragweed and certain grasses; asthma, due to the proteins from animal hair and fowl feathers, etc.; and urticaria or hives, produced by certain articles in the diet.

Allergens are extracts prepared from the proteins of various substances and are used to determine the susceptibility of the patient to proteins and to prevent and relieve the conditions caused by hypersensitiveness.

The patient's susceptibility is tested by rubbing a small quantity of the allergen into a scratch in the skin. If the patient is sensitive to that particular protein, an urticarial wheal or elevated red spot results.

Prevention and Treatment of Allergy.—When the identity of the particular protein causing the symptoms has been determined, the attacks of the disease may frequently be prevented by removing the causative factor; in urticaria, by omitting certain foods from the diet; in asthma, by modification of the diet, by eliminating pet cats and dogs or removing the hair mattress or the feather pillows, etc.

In hay fever the patient may have to be immunized against the specific pollens causing the attack. This process is called desensitization.

sitization. It consists of a series of ten or more injections of dilute solutions of the specific pollens in graduated strengths given at intervals of about five days. The treatment should be begun sufficiently early so that the maximum dose is reached by the time of the first attack of the disease, and this dose is repeated once a week during the pollen season. Immunity lasts only about a year. In some cases of asthma and urticaria the patient may be desensitized to the specific proteins causing their symptoms.

Allergic Reaction

Occasionally a hypersensitive patient may show symptoms of coryza, asthma and urticaria after an injection of one of the larger doses of allergen solution. Too short an interval between doses increases this possibility. The reaction occurs in from five to thirty minutes after the injection and is promptly controlled by one or more injections of adrenalin 1:1000. The dose is 6 to 10 minims and may be repeated in ten minutes if necessary.

Preparations

Pollen antigens include ragweed, timothy, goldenrod, dandelion and various grasses.


Food allergens include cereals, milk, egg, sea foods, nuts, fruits, vegetables, meats and condiments.

Animal hair allergens include the extracts of hair and dander of cats, dogs, rabbits, horses, cows, etc.; the feathers of chickens, ducks and geese; and various furs.

Bacterial allergens are extracts of dried bacteria, such as staphylococci, streptococci, pneumococci, etc.

Group allergens are mixtures of several specific proteins, usually five. They are used for testing. A positive group test indicates that the patient is sensitive to at least one protein of the group, and testing with individual allergens is then resorted to.

Most of the allergens come in two forms, as a powder or liquid of high concentration for diagnosing, and in ampules for desensitizing.



UNIT XIV

CHAPTER XXIII

HISTORY OF MATERIA MEDICA

The story of materia medica is as old as the story of man, for sickness has been man's heritage from the beginning of time and the search for ways and means to combat disease, one of his earliest and most persistent activities. Early man's first experiments in dealing with disease were suggested by the belief common to all primitive people that the world in which they live teems with invisible spirits, some of whom are good and some bad. Whatever puzzled them in nature was attributed to these supernatural agencies, and it followed that disease was at first thought to be an evil spirit or the work of such a spirit. If this supposition were true, the logical treatment was obviously to placate and cajole the invader by burnt offerings and sacrifice, or frighten it away by assuming a terrifying aspect, resorting to hideous noises, or by administering foul-tasting substances, all of these measures being designed to make the body an uncomfortable habitat for the spirit. The search for obnoxious materials soon led man to experimentation with the herbs of the field and the forest, and as the knowledge gained from experience increased, the first rudiments of materia medica were assembled. These more or less intuitive efforts of primitive man led to some valuable discoveries. Savages in widely separated countries know the properties of the most fatal arrow poisons, such as curare, veratrine, and ouabain, as well as the virtues of drugs like opium, hashish, hemp and tobacco. Centuries ago the native Indians of Peru discovered the value of cinchona bark for the treatment and prevention of malaria, and the natives of Brazil recognized the worth of ipecac for amebic dysentery. The victims of leprosy in the Far East have apparently always known that they received relief by rubbing their wounds with chaulmoogra oil, and to them we owe the use of this drug as a specific for the loathsome disease. The Indians of our own country used arbutus for rheumatism; lobelia for coughs and colds; wild sage tea, goldenseal, and flowering dogwood for fevers; elders, wild cherry, and sumac for

colds and quinsies; inhalations of pennyroyal for headache; sassafras leaves for wounds and felons, and the roots of sassafras for cooling and purifying the blood.

As the medical lore of the savage accumulated, there appeared within the tribe individuals who demonstrated a special talent for herb-doctoring, bone-setting and rude surgery, and who employed it as a special means of earning a livelihood. They were either the wise-women who sought by their art to lessen the hardships and dangers of childbirth, or certain tribesmen of superior intelligence and cunning, who, appreciating the credulity of the rank and file, made free use of incantations and charms in their therapeutics and established themselves in the community of their superstitious neighbors in the dual rôle of priest and physician. These nature healers or specialists soon perceived not only what substances are good and what are harmful, but that a number of poisons are also remedies under certain conditions. This drug and poison lore was the beginning of materia medica and medicine.

ANCIENT PERIOD

Egypt

The oldest historic phase of medicine is the Egyptian. The main sources of data are the medical papyri, the most important of which is the Ebers papyrus, written in the sixteenth century B.C. It is in the form of a scroll twenty-two yards long and about twelve inches wide and contains a collection of prescriptions and formulas covering a wide range of uses. Included among them are many invocations and conjuring forms for driving away disease, as well as specific recipes, calling in many instances for drugs which are in common use today; for example, aloes, castor oil, figs, vinegar, turpentine, opium, wormwood, peppermint, and squill.

Among the mineral and metal substances used by the Egyptians were iron, copper sulfate, magnesia, niter, sodium carbonate, and salt, and precious stones ground into powder.

The animal preparations included such extraordinary substances as lizards' blood, swine's teeth, putrid meat, stinking fat, milk, goose grease, asses' hoofs, animal fats, excreta of various animals, and of flies (a soothing syrup for babies was made of the latter), and such weird ingredients as the thigh bone of a hanged man or the moss grown on a human skull.

The prescriptions called for purges, headache remedies, tonics, hair restorers, and remedies for hookworm, tapeworm and intestinal

worms, to be put up in the form of pills, powders, infusions, decoctions, gargles, salves, plasters, poultices, and confections. Over seven hundred drugs are mentioned and one prescription required thirty-five ingredients.

As the inclusion of invocations and charms in the prescriptions would imply, medicine was closely allied with religion, as it was to remain for many centuries. The doctors were all priests paid out of the royal treasury, but they were allowed to take fees also.

Greece

The pharmaceutical history of Greece begins with the legends regarding its gods and goddesses. The reputed activities of these mythical characters are so inextricably woven with the authentic doings of real men and women that it is often hard to determine where legend ends and history begins. The story goes, however, that Chiron, the centaur, originated the pharmaceutical art and imparted his valuable knowledge to Aesculapius, son of Apollo. Aesculapius, with the aid of his daughters Hygeia and Panacea, in turn taught mortals the art of healing, but he became so successful in combating disease that he incurred the wrath of Pluto, god of the underworld, because he was diminishing too greatly the number of shades received in Hades. Pluto prevailed upon almighty Zeus to destroy Aesculapius with a thunderbolt, but upon the intercession of Apollo, Zeus deified him as the god of healing. His mortal followers in time made up the organized guild of physicians called Aesclepiades. They built temples in his honor in which they practiced their art and increased their knowledge of healing. These temples were situated in hills or mountains, usually near mineral springs, and were managed by trained priests. Hence they were virtually popular sanatoriums or hospitals for the sick. The patient was received by the physician priests and after spiritual purification by prayers and sacrifice, was further cleansed by a bath from the mineral springs, catharsis, massage and inunction, and encouraged with medicated wines and soft music to sleep and to dream. The priest then interpreted the dream as a message from Morpheus, and offered medical advice accordingly. If the treatment was a success and the patient recovered, a votive tablet giving the history of the case and the treatment was hung in the temple where anyone who wished might consult it. In this way, a considerable body of empirical knowledge was assembled and these Temples of Health took on some of the characteristics of a medical school. The most celebrated ones were at Chnidus and Cos.

The most famous representative of the Aesclepiades was Hippocrates, who was born in the Island of Cos 460 B.C., of a long line of priest physicians, and was reputed by popular tradition to be the seventeenth in direct descent from Aesculapius. Hippocrates pursued his early studies at Cos and Cnidus but later came under the influence of the great thinkers and philosophers of the period and soon began to give to medicine their scientific and ethical ideas. He denounced the belief in the supernatural origin of disease and the use of charms, incantations and other superstitious devices of priestcraft and substituted the doctrine that disease was due to natural causes and that knowledge of it would be gained only through the study of the natural laws. He taught the use of the senses in collecting data for diagnosis, and the use of inductive reasoning in arriving at diagnostic conclusions.

His therapeutic measures were decidedly modern. He believed that the body has great power to recuperate and that the rôle of the physician should be simply to aid Nature in her work. His treatment consisted usually of fresh air, good food, purgation, blood-letting, massage, and hydrotherapy. Although he mentioned over four hundred drugs in his writings, he used only a few of the important ones, among them opium. His preparations included fomentations, poultices, gargles, suppositories, pills, lozenges, ointments, cerates, and inhalations.

Hippocrates is called the Father of Medicine because his influence has extended through the ensuing ages and his teachings established the sound principles which control the practice of medicine to the present day.

Another early Greek physician was Dioscorides, who was an authority on materia medica. He described six hundred plants and plant principles of which no less than seventy-four are in use today. His work was the chief source of pharmaceutical knowledge of antiquity.

Rome

After the Roman conquest of Greece, Greek medicine migrated to Rome. The most famous Greek physician of this period was Galen (A.D. 131-201). He based his teachings and practice very largely upon the work of Hippocrates and established a system of medicine and pharmacy which made him the supreme authority for several hundred years. He originated many preparations of vegetable drugs which even now are spoken of as galenicals, and was the first to prepare rosewater ointment or cold cream.

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dates five hundred years before the invention of printing. Mistletoe was a great panacea. Lycopodium, clover, primrose, henbane, and verberna were common remedies, also wormwood, belladonna, hellebore, and mandragora.

During this period, we have the first record of the use of some of the remedies used in modern practice. In the sixth century, Alexander of Tralles used colchicum for gout, iron for anemia, cantharides as a blister, and rhubarb for dysentery and liver complaints.

Arabian Influence

In the eighth century the Arabs spread over the Holy Land, Egypt, North Africa and Spain, and began a supremacy which lasted over five hundred years. They were especially interested in medicine, pharmacy, and chemistry, and built hospitals and schools for the pursuit of their study. They carried forward the knowledge obtained from Greece and Rome and preserved the pharmaceutic art from the sixth to the sixteenth centuries. Their medicine was a composite blend of the practice of the Greeks and Jews and of the astrology and occult lore of Egypt and India. The teachings of Hippocrates and Galen, which had been translated into Arabic in the seventh century, furnished much of their material.

The Arabians contributed many new drugs. We are indebted to them for use of senna, camphor, rhubarb, musk, myrrh, cassia, tamarind, nutmeg, cloves, cubeb, aconite, ambergris, cannabis, and sandalwood. They were the originators of syrups, juleps, alcohol, and aromatic water. They introduced into Europe the decimal notation, acquired by them from a now forgotten race in India.

The first great Mohammedan author was Geber, who wrote exclusively on chemistry. He is the reputed discoverer of sulfuric acid, nitric acid, nitrohydrochloric acid, corrosive sublimate, and lunar caustic.

Avicenna was an accomplished physician of the tenth century. He wrote the *Canon*, a miscellaneous collection of past medical lore with his interpretations. His works were considered authoritative in universities as late as 1650.

During this period, pharmacy was practiced somewhat as a profession separate from medicine. The first apothecary shops were established and the first pharmaceutic formulary or set of drug standards was produced. This served as a model for the first London pharmacopoeia. The Arabian pharmacists were called sandalini

MEDIAEVAL PERIOD (A.D. 400 to 1500)**Early Period—The Dark Ages—A.D. 400-1100**

The term *Middle Ages* is given to that period of European history which lies between what are known as ancient and modern times, extending from about the middle of the fifth to the middle of the fifteenth century. The historical event which marked the close of ancient times was the decline and fall of the Roman Empire. This process extended over three or four centuries, during which period successive hordes of Germanic barbarians poured in from the north and east and overran Western Europe. They succeeded gradually in wresting the territory piecemeal from the Romans and in setting up their own tribal organizations. This process of dismemberment of the Roman Empire was completed in the fifth century and was followed by a period of about six hundred years known as the Dark Ages, because during this time the old civilization was largely destroyed and there was very little progress in learning. The German tribes were slowly learning to combine their primitive institutions with those of Rome and were assimilating the first rudiments of culture through their contact with the Latins. Wars between the tribes were frequent and served to stifle all effort along constructive lines. Their medicine was folklore and tradition, the employment of wonder-cures and temple sleeps similar to those of the Greeks before the advent of Hippocrates.

Another important movement which was in progress at the same time was the spread of Christianity. After more than three centuries of struggle and persecution, the Christian church triumphed in 311 through a decree of the emperor which made it the official church of Rome. Thereupon, religious orders arose whose members scattered throughout Europe preaching the new doctrine and building monasteries, where they could withdraw from the world and devote their lives to the work of the Church. The monasteries, particularly those of the Benedictines, soon became the repositories of all the learning of the period. The monks collected all available manuscripts and copied and preserved them. Among other things, they preserved the works on pharmacy and medicine. Since it was part of their religious duty to give aid to the sick and needy, they controlled most of the practice of medicine and disseminated much knowledge of healing. Their treatment was usually good food, quiet, rest, and the administration of decoctions of simples from their gardens. Monastery gardens were an important factor in the development of herbals or books of plant lore, the oldest of which

dates five hundred years before the invention of printing. Mistletoe was a great panacea. Lycopodium, clover, primrose, henbane, and verberna were common remedies, also wormwood, belladonna, hellebore, and mandragora.

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and their stocks were regularly inspected and punishment was meted out to those found guilty of selling spurious or deteriorated drugs.

Rise of Universities

The word university means an association and the principal universities of Europe had their origin in the voluntary association of guilds of students banded together for mutual protection and established at some place favorable to the pursuit of their studies. Salerno, which was founded in the eighth century, was the first of the educational institutions of the university type. Others founded later were the University of Paris, 1110; Bologna, 1113; Oxford, 1167; Cambridge, 1209, Padua, 1222; and Naples, 1224. They exerted a great influence upon the development of all science, and especially of medicine and pharmacy. Pharmacy was taught in all as part of the medical course. One of the most eminent pharmaceutical authorities of this period was Nicholas of Salerno, Director of the Medical School. He wrote the *Antidotarium* which was the standard for pharmaceutical preparations for centuries. It contained the basic units of the present apothecaries' system, the grain, scruple, and drachm, just as they are used today. At Salerno, the study of anatomy was resumed under a decree which permitted the dissection of a human body every five years. Didactic instruction here was based upon Hippocrates, Galen, Avicenna, and the Antidotary of Nicholas Praepositus. A famous woman physician, Trotula of Salerno, first used mercury in the treatment of syphilis.

LATE MEDIAEVAL PERIOD

In 1095 occurred the first of the Crusades, which extended over a period of nearly two hundred years, and exerted a profound influence on pharmacy, by bringing about a fusion of Arabian science and learning with the primitive practices based upon folklore and tradition in Central and Northwest Europe. Records of the custom-house of the port of Acri in Italy in the early thirteenth century show large traffic in the various spices, opium, and rhubarb. Venetians brought the first sugar to Europe during the time of the Crusades. It was costly and was used exclusively as medicine, as were most of the spices.

The fourteenth and fifteenth centuries witnessed a great awakening of interest in medicine and pharmacy throughout Europe. The Moors of Spain, who had a great reputation for knowledge and skill in these branches of science, and who had been driven out of Gra-

nada by Ferdinand in 1492, scattered over Europe, practicing and teaching. Moreover, during this period, epidemic diseases were very prevalent, especially leprosy, ergotism, and Black Death. The Black Death (bubonic plague) swept away 25 per cent of the human race or 60 million people during this period. Pharmacies as separate places for compounding and dispensing medicines spread through Europe with great rapidity during the thirteenth century.

In the fifteenth century alchemy, brought in by the Arabs, swept over Europe like a conflagration. Alchemy was the search for means of transmuting base metals into gold. The mere desire to discover such a substance gave rise to a universal belief that one existed and the "philosopher's stone," as this elusive substance came to be known, was as much a reality to the alchemist as the actual substances with which he worked. Gradually belief spread that the philosopher's stone could not only transmute all metals into gold but could also cure all diseases, restore youth, and indefinitely prolong life. It thus became also the Elixir of Life. While the alchemists were carrying on the search for the stone, they made important inventions and discoveries which laid the foundations of the modern science of chemistry. In 1438 printing was invented and the world was flooded with books. One of the earliest printed works extant contains an illustration of a fifteenth century pharmacy.

SIXTEENTH CENTURY

In the sixteenth century, pharmacy came into its own. Drugs were rare and costly, prescriptions were complex, and special art was required in preparing and keeping the drugs. Formularies appeared in such numbers that a need was felt for an authoritative standard. This was furnished by Valerius Cordus, son of a professor of medicine at Marburg. Cordus collected formulas during twelve years of teaching at Wittenberg and compiled these in manuscript form. The physicians of Nuremberg wished a copy for the local druggists and secured the consent of the senate in 1546 to have it printed. This work of Cordus was the first pharmacopoeia to be printed and authorized for use in a community for the sake of uniformity. It drew its material from Greek, Roman, and Arabian sources and quoted freely from Galen, Dioscorides, Avicenna and Nicholas Praepositus. It contained comparatively few types of preparations: namely, aromatics, opiates, confections, conserves, purges, pills, syrups, plasters, cerates, troches, salves, and oils. Editions

were published in Paris, Lyons, Venice, and Antwerp. It held its place till 1666 and was revised five times meanwhile.

The outstanding figure of the sixteenth century was Paracelsus, the son of a German physician and chemist. At the age of sixteen, he began the study of medicine at the University of Basle but soon gave it up to experiment with chemistry and alchemy. He traveled widely, gathering a vast amount of knowledge, especially of folk medicine, from barbers, gypsies, and others with whom he associated. He served some time as a military surgeon in the Low countries and worked in mines in the Tyrol. Here he investigated processes of preparing metals and made experiments as to their medicinal virtues. His cures gained wide publicity and he was called upon to prescribe for many of the great men of his day. In 1526 he was appointed professor of physics and surgery at Basle. Here he inaugurated his career as a teacher by publicly burning the works of Galen and denouncing the Arabian masters whose doctrines were then generally followed. He also flouted tradition by lecturing in German instead of Latin. His defiance of tradition and his arrogant manner aroused the enmity of the other members of the faculty and he was compelled to leave the university in 1528. He resumed his wanderings. At Salzburg, he gave offense to a prominent physician and was thrown from a window by the man's servants, dying from the fall.

In spite of his objectionable methods, Paracelsus exerted a profound influence upon the medical beliefs of his time and of succeeding centuries. He attacked the weak points of the prevailing system of medicine; he destroyed the "humoral pathology" which taught that diseases were due to an excess or deficiency of the "humors," bile, phlegm, or blood, and substituted the doctrine that diseases were actual entities to be combated with specific remedies. He improved pharmacy and therapeutics, introduced some new remedies such as calomel and sulfur, made some new chemical compounds and strove to reduce the overdosing then practiced.

SEVENTEENTH CENTURY

In 1618 the first London Pharmacopoeia appeared. It was chiefly a compilation of older authorities. It was sponsored by the London College of Physicians and its use was made obligatory throughout the British realm by a decree of King James. It was very large compared with the modern pharmacopoeia, containing 1028 simple drugs and 932 preparations and compounds. The most complex

preparation contained 130 ingredients. One substance listed was usnea. This was moss from the skull of a man who had died a violent death. It was not hard to obtain in England in those days because the bodies of criminals who had been executed were suspended in chains in public places as a warning to other criminals, and the exposure was conducive to growth of moss on the skull.

Great interest was displayed in chemistry and pharmacy in this century, and many preparations originated then which are still in use. Among them were the infusion of senna or black draught, the alcoholic tincture of opium or laudanum, the compound tincture of benzoin, the balsams of Peru and Tolu, guaiacum, sarsaparilla, and jalap. In 1638 cinchona was imported by the Countess of Cinchona, wife of the Viceroy of Peru, who had been cured of a severe intermittent fever by its use. Coca was likewise introduced from Peru, and ipecac found its way into Europe and was used with such skill by a certain quack named Helvetius that Louis XIV paid him \$4,000 for his secret.

EIGHTEENTH CENTURY

The eighteenth century likewise witnessed great progress in pharmacy. A German practitioner by the name of Hoffmann originated the elixir of orange and Hoffmann's anodyne. A Berlin apothecary identified magnesia, the alums, the potassa and soda and discovered beet sugar. A French pharmacist published an essay entitled "The Superstitions Concerning the Philosopher's Stone" and thereby helped divert alchemy into more profitable channels. In 1775 Louis XVI paid nearly \$5,000 to a certain Madame Nouffer for a celebrated cure for tapeworm. She inherited the secret from her husband, a Swiss physician. The drug proved to be male fern, commonly known since Galen.

Inoculation against smallpox was introduced in the latter part of the eighteenth century by Edward Jenner, an English physician. He had been studying for years on the subject of smallpox, swinepox, and cowpox and the development of the two latter diseases when communicated to man, and had noticed that milkmaids who were frequently infected with cowpox were immune to smallpox. He finally inoculated his own son with swinepox and ascertained that the child was proof against smallpox. He made his first public inoculation with vaccine on May 14, 1796, and within a year had won the confidence of the physicians in his theory of immunization.

In 1785, the infusion of digitalis was introduced by William Withering of England for the treatment of heart disease. The foxglove is carved on Withering's monument.

Dover's powder had its origin about this time. Thomas Dover administered the drug in doses of sixty grains and claimed to have given 100 grains. This was equivalent to ten grains of opium and ten grains of ipecac. The pharmacists in filling his prescriptions usually advised patients first to make their wills.

A great number of important pharmacopoeias and works of reference appeared during the century. One of particular interest was the dispensatory of the London hospitals, St. Thomas', Guy's, and St. Bartholomew's, 1741. It listed viper's flesh as an ingredient of one preparation, and wood lice of several. Dried horses' hoofs were used to check the spitting of blood. The motto of the book was, "Prepare to die, for behold, Death and Judgment is at hand."

NINETEENTH CENTURY

During this century, chemistry gradually takes its place as a highly specialized science, with pharmaceutical chemistry as an important subdivision. The first great pharmaceutical discovery was that of the alkaloid morphine obtained from opium by a German apothecary, Serturner, in 1815. This was the first active principle to be isolated and led to enthusiastic research on many vegetable drugs. The result was the discovery of quinine, strychnine, and veratrine by Pelletier and Caventou; of emetine by Pelletier and Majendie; of atropine by Brandes, and of codeine by Robiquet. All of these men were pharmacists. Their discoveries made it possible to administer drugs in a form which was attractive and palatable and which made possible the accurate study of dosage.

• In 1842 Dr. Crawford W. Long of Georgia first used ether as a general anesthetic and in 1847 Sir J. T. Simpson used chloroform for the same purpose.

About 1856 appeared the first of the numerous coal tar products. Perkin, in a vain attempt to produce synthetic quinine, discovered instead the first coal tar dye, called after him "Perkin's purple" or mauve. This led to the preparation in the laboratory of a great family of remedial agents, some of which, such as salicylic and benzoic acids, duplicated products previously obtained from natural sources, and others of which were new to science; for example, salicylic acid and antipyrin.

The discovery of so many new drugs and the invention of new and convenient dosage forms led to the establishment of large scale manufacturing plants which took over much of the work formerly done by the pharmacist with his mortar and pestle.

This century witnessed also the initial appearance of the important national pharmacopoeias. The French Codex was first to be produced. It was issued in 1818 and contained one remarkable item, a formula for an extract of opium in which the preparation was to be boiled incessantly for six months and the water lost by evaporation to be constantly replaced. The first pharmacopoeia for the United States appeared in 1820, the national standard for Great Britain in 1864 to replace those of London, Edinburgh, and Dublin, and that for Germany in 1872, superseding nearly a score of local volumes.

Fewer drugs were prescribed and such prescriptions as were given were accompanied with greater knowledge of their expected action. In other words, rational medicine began to replace empiricism. During this period purging and bloodletting became less popular and definite action toward exposing harmful patent medicines and nostrums was taken.

RECENT PROGRESS

Great progress has been made in pharmacy and medicine since this century began. In pharmacy, growth has been chiefly along the lines of strengthening and improving the work of the professional organizations such as the American Pharmaceutical Association and the National Association of Retail Druggists, and with the promotion of legislation controlling the manufacture and sale of drugs. The most important acts were the Food and Drug Acts of 1906 and 1938 and the Harrison Anti-Narcotic Act of 1914.

It is said that more progress has probably been made during the past fifty years than in all the years prior to that time. As far as therapeutics is concerned this is largely due to changes in the concept of the cause of disease. When it was believed that evil spirits caused disease, the treatment given was highly varied and used in the hope that one of the measures resorted to would be the right one. Since the acceptance of the germ theory there has been a rapid advancement in scientific method of research. Such method has been greatly aided by animal experimentation, appropriation of money for research work, efforts of public health organizations to educate the public and to collect valuable vital statistics.

FUNDAMENTAL THERAPEUTIC DISCOVERIES

INTRODUCTION INTO MEDICINE

Digitalis	1785
Morphine	1815
Iodides in Syphilis	1836
Ether Anesthesia	1842
Chloroform Anesthesia	1847
Antiseptics in Surgery	1865
Iodoform	1879
Coal Tar Antipyretics	1884
Cocaine	1884
Acetyl Salicylic Acid or Aspirin	1900
Barbitals	1904
Arsphenamine	1907
Iodine in Goiter	1911
Insulin	1922
Sulfanilamide	1935
Sulfapyridine	1936
Gramicidin	1940
Penicillin	1941

Of interest to both pharmacy and medicine are the many biologic preparations such as the vaccines, antitoxins and sera now in common use and the valuable group of anesthetics which is constantly growing through the isolation and duplication in the laboratory of more and more of the potent vegetable substances found in nature. The introduction into medicine by the German physician Ehrlich in 1907 of salvarsan, the great specific for syphilis, and the discovery by Banting in 1922 of insulin for the treatment of diabetes, constitute two of the epoch-making events of the century.

With the increased knowledge of drugs has grown an increasing awareness of implications in their misuse and overuse. Among other trends in modern medicine is the use of other therapeutic agencies either to supplement drug therapy or to replace it. Such therapies would include vitamin therapy, diet therapy, and various kinds of physical therapy.

To discover chemotherapeutic agents which will be effective in every infectious disease is one of the goals of research workers in medicine. However, for years there were only a few chemicals which acted as specifics. Among the most important were quinine for malaria and the arsenicals for syphilis. In the last few years two remarkable chemotherapeutic agents have changed chemical therapy tremendously. Infections which a few years ago took a tremendous toll in sickness and deaths are now well controlled by

the sulfonamides and penicillin. In 1908 sulfanilamide was first prepared by Gelmo, a German organic chemist, who was investigating azo dyes. It was not until 1932, however, that its possible therapeutic value was realized. In 1932 prontosil was patented in Germany by Klorer and Mietzsch. A German worker, Domagk, is credited with the discovery of the therapeutic value of prontosil. In 1932 Domagk observed that mice with streptococcic septicemia could be protected by prontosil. It was later shown that prontosil breaks down into para amino benzene sulfonamide which is the effective substance. In the next few years more and more interest was aroused in these drugs, and today they have a rightful place as some of our most important drugs. Para amino benzene sulfonamide was accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in N. N. R. in 1937, at which time the name of sulfanilamide was suggested for it. Since then many new sulfonamide derivatives have been tried, and a few of them have become well established in drug therapy.

The story of the recent development of antibacterial agents of biologic origin or antibiotics is one of the most interesting new developments in pharmacy. In 1929 Dr. Alexander Fleming at the University of London noted that a mold which contaminated a plate of Staphylococci produced a zone of inhibition around it in which the Staphylococci did not grow. Fleming found that the mold, *Penicillium notatum*, secreted into its medium an antibiotic agent which he named penicillin. He found it was not toxic to animals, did not hurt white blood cells, and that it inhibited the growth of certain gram-positive pathogens. He used broth containing penicillin clinically on several cases of skin infections with favorable results. However, little was done clinically about it for the next ten years.

In 1939 Rene J. Dubos of the Rockefeller Institute for Medical Research published the results of experiments done on certain bacteria found in the soil. Dubos acted on the assumption that all organic matter added to the soil would eventually undergo decomposition by microorganisms. Samples of soil were incubated for a few weeks to bring about decomposition of most of the organic matter present. Then cultures of Staphylococci, Group A hemolytic streptococci, and Pneumococci were added to the soil at intervals.

After two years, a gram-positive, spore-bearing aerobic bacillus capable of lysing the living cells of many gram-positive bacteria was isolated from the soil. The soil bacillus, called *Bacillus brevis*, produced a substance destructive to certain gram-positive bacteria. The

destructive substance could be extracted from the bacteria. It was named tyrothricin, and was later shown to be composed of two substances, gramicidin and tyrocidine. Gramicidin is much more effective than tyrocidine therapeutically. Unfortunately, gramicidin is hemolytic and so must be used only for local infections, never where it can get in contact with the blood.

Our story now turns back to penicillin. In 1938 Dr. Howard Florey at Oxford University began to study penicillin and other naturally occurring antibacterial agents. Dr. Florey and his associates are responsible for the isolation of penicillin, its assay and dosage and for proof of its usefulness clinically. The first patient was treated with penicillin early in 1941. Because of the war it was impossible to start large scale production in England. Dr. Florey came to the United States in 1941 and asked for the help of the National Research Council in studying penicillin. Production was soon started in the United States, and the first patient in this country was treated with penicillin in March, 1942.

It should be noted that obtaining antibacterial agents from natural sources is not a new procedure. There are many such substances throughout the plant and animal kingdoms. Quinine, which is produced by a plant has been used for many years. One of the most important factors in discovering chemotherapeutic agents is that they give to research workers important clues for the understanding of chemotherapeutic agents. When the action of a chemotherapeutic agent is understood, whether it be of chemical origin (as are the sulfonamides) or of biologic origin (as is penicillin), the making of new chemotherapeutic agents and the proper use of those already known will be best accomplished.

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CHAPTER XXIV

DRUG LEGISLATION

There has always been a need to protect the consumer and patient against the unscrupulous use of reliable drugs and the drugs of unreliable manufacturers. However, this need has been greatly increased in the past several decades. The zeal with which advertising campaigns have been conducted, the multiplicity of means by which information reaches the public, the startling discoveries of medical science, especially in the realm of vitamins and endocrinology, the complexity of today's mode of living with its responsibility for the tremendous increase in the consumption of medicines whether purchased with or without a physician's prescription. All demand measures of control.

Federal Food and Drug Act

The Food and Drug Act, first passed in 1906 and amended in 1938, is designed to put an end to the adulteration of crude materials, to reduce to a minimum the sale of inferior drugs, to make it compulsory for the manufacturer to label his products honestly and to declare the presence of certain dangerous ingredients so that the consumer will know what action to expect from its use. The law also specifies that any name listed in the *United States Pharmacopoeia* or *National Formulary* shall be made according to the directions in these books. The *National Formulary* thus takes its place with the *Pharmacopoeia* as a legal standard.

Power for enforcement of this act is placed in the Department of Agriculture in a division made up of pharmacists, chemists, bacteriologists, physicians, and other experts. Advertising relevant to food and drugs was not considered in the original act but has been in the Wheeler-Lea amendment.

Features of the new law which may be of most significance and interest to the nurse are:

- a. Control is extended not only over the drugs used for the prevention, cure, or mitigation of disease but also over those used for diagnosis and those which affect the structure and function of the body.

- b. All cosmetics except soap and certain coal tar dyes are subject to certain regulations. Cosmetics cannot contain substances which are harmful when used as indicated on the label. The contents of cosmetics need not be listed as is true of compounded drugs but false or misleading labels are outlawed. If certain coal tar dyes are used, there must be adequate warning on the label regarding its danger.
- c. The labels on laxatives must carry a warning as to their use when persistent abdominal pain is present.
- d. The name, quantity, and percentage of seventeen hypnotic, narcotic, and habit-forming substances must be indicated on the label. These are alpha- and beta-eucaine, barbituric acid, bromal, cannabis, carbromal, chloral, coca, cocaine, codeine, heroin, marihuana, morphine, opium, paraldehyde, peyote, and sulfonmethane. Such a prescription must also include this statement, "*Warning, may be habit forming.*"
- e. When any of the following are present in a preparation the name, quantity, and percentage strength must be indicated: acetanilid, aminopyrine, arsenic, atropine, bromides, chloroform, digitalis, ether, hyoscine, hyoseyamine, mercury, ouabain, strophanthin, strychnine, and thyroid.
- f. The amount, kind, and proportion of alcohol in a preparation must be stated.
- g. Provision is made for the thorough testing of new drugs before they are placed on the market. Exemption is made for their use by qualified experts who investigate their therapeutic use and value.
- h. A drug is falsely branded unless it has adequate warning against its use in pathologic conditions or by children in whom its use may be dangerous to health.
- i. Traffic in food which is injurious to health is prohibited. Special dietary foods must have on their labels full information concerning the mineral, vitamin, and other dietary content.

For other details of this law about which the student may wish to have information, the *Journal of the American Medical Association* is recommended.

Vaccines, Serums, Toxins

The supervision of vaccines, serums, toxins, etc., is under the control of the United States Public Health Service. Laboratories for the manufacture of these products must be licensed by the Public

Health Service whose inspectors visit them periodically and test their products to determine the amount of preservative which they contain and to ascertain whether they are free from bacterial and toxic contamination. Several preparations have been standardized by the Public Health Service and the manufactured products must conform to this standard. These preparations include diphtheria antitoxin, tetanus antitoxin, antimeningococcus serum, diphtheria toxin-antitoxin, diphtheria toxin for the Schick test, diphtheria toxoid, rabies vaccines, and scarlet fever streptococcus antitoxin.

Harrison Narcotic Law

The Harrison Law of 1914 (amended 1917) regulates the importation, manufacture, sale, and use of opium, and cocaine, and all their compounds and derivatives, with a view to checking and preventing their indiscriminate use and the spread of the drug habit.

It provides that every wholesale and retail druggist and every physician and dentist selling or prescribing these drugs must register with the Department of Internal Revenue and pay an annual registration fee. Druggists are permitted to sell these drugs only to persons registered under this law and must use special record blanks issued by the Commissioner of Internal Revenue. They must keep a record of each sale and give a duplicate to the purchaser. These records must be kept for a period of two years and are subject to inspection at any time by the revenue official. Physicians must keep a record of the amount and disposal of the drugs they obtain. A prescription for substances named in the law must bear the physician's name, address, and registry number, the name, age, and address of the patient, and the date on which the prescription was written. It is unlawful for the pharmacist to refill the prescription.

Any violation of the law makes the offender liable to a fine of not more than \$2,000 or imprisonment for not more than five years or both.

Application of the Harrison Law in Hospitals

Every hospital must register with the Department of Internal Revenue and conform to the same regulations as physicians. All drugs which are listed under the Harrison Law must be ordered for ward use on special blanks which bear the hospital registry number and the signature of a physician. Every order for a patient which involves one of these drugs must be signed by the physician who orders it, both in the order book and on the patient's chart. A rec-

ord specially reserved for this purpose is kept in every ward, in which the nurse records the name of the patient, the date of administration, the drug given, and the amount. In this way, she is able to account for the quantities of these drugs received from the pharmacy.

Drugs Listed Under the Harrison Narcotic Act

I. Opium, Morphine and Derivatives:

Extract of Opium	Pantopon
Powdered Opium	Dilaudid
Ipecac and Opium (Dover's Powders)	Narcotine
Tincture of Opium	Papaverine
Morphine Sulfate	Papaverine Sulfate
Morphine Hydrochloride	Papaverine Hydrochloride
Magendie's Solution	Apomorphine Hydrochloride
Codeine Sulfate	Stypticin
Codeine Phosphate	Styptol
Codeonal	
Heroin	
Dionine	

II. Coca, Cocaine and Derivatives:

Fluid Extract of Coca	Tropacocaine
Cocaine	Eucaïne
Cocaine Hydrochloride	Holocaine

Narcotics prescribed in small quantities are exempt from the federal law if the prescription does not contain more than any one of the following per fluid ounce. two grains of opium, one-fourth grain of morphine, one-eighth grain of heroin, or one grain of codeine. Certain states, however, have laws which include some of the above-mentioned preparations of opium. For example, some states have regulations whereby the sale and dispensation of paregoric is under the same restriction as other drugs listed in the Harrison Law.

Besides the two federal laws discussed here various states have statutes applicable to the manufacture and sale of drugs within that state. Outstanding among these are the regulations for the sale of the barbiturates, or the "Lullaby Laws" as they are popularly called. The necessity for such laws is understood when the student studies these drugs, but it is not amiss at this point to mention that this group of sedatives and hypnotics was responsible for close to three hundred suicidal deaths in 1936, and the records show this number to be on an upward trend.

of

Note to Nurse:—

Chart in whole numbers not in fractions. Chart number of tablets given not dosage ordered. Total the amount given during the twenty-four hours each day. Save all sheets and send down to the Pharmacy the first of each month to be filed away for the inspection of the "Federal Narcotic Agent." N.B.: Tablets wasted are to be charted as wasted, and signed by the nurse.

Chart in Ink Not Pencil

[illegible]

The narcotic record blank above is an example of how narcotics may be accounted for in a hospital. Record forms may vary somewhat in the way they are set up, but they must contain certain definite information as indicated in the headings of the sample shown. No special record form is prescribed. Hospitals and institutions must keep records in the manner best calculated to meet the conditions existing therein so as to enable an inspecting officer to see quickly the kinds and quantities of narcotics used daily.

The necessity for detailed accuracy in keeping these records cannot be overemphasized. It is only by honest, meticulous recording by the individual nurse that the collective records of the hospital pharmacy are meaningful. It is almost impossible, but necessary, to account for a lost tablet of an opiate weeks after its loss occurred. The nurse who understands the reasons for such records will undoubtedly do her share in keeping them.

The laws so far discussed illustrate the progress made toward the goal stated at the beginning of this chapter—namely, the protection of the patient and consumer. Several other problems still need to be dealt with and in each of these the nurse, whether student or graduate, can render valuable assistance.

It is well to remember that the effectiveness of legislation in this regard will depend not only upon the vigorousness with which laws are enforced by the proper authorities, but also upon the cooperation between interested professional and lay groups. That such efforts to date have been worth while is evident in the fact that, while the sales of medicines in general increased \$36,000,000 for 1939 over 1937, the sale of proprietary and "patent" medicines for the same period decreased \$18,000,000.

The indiscriminate use of drugs may have several consequences. The contents of the drug may be harmful, and it is well to recall at this point that individuals may have untoward reactions and idiosyncrasies to drugs. Or, the active ingredients of a remedy may not be harmful but they may be entirely useless. Such self-medication may mask symptoms of serious disease and thus delay treatment or render it futile. For example, baking soda and similar common antacids indiscriminately used may relieve the symptoms of gastric ulcer temporarily, but the progress of the disease is not checked. Cancer "cures" are extremely vicious, and the continued use of cathartics may not be without serious consequences. As long as it is possible to obtain medicines without a physician's prescription it will be necessary to continue an educational campaign against "self-medication."

"Patent" medicines are quite generally a waste of money. The discrepancy between their actual cost and the selling price is great. The same amount of money expended for reliable medical care would yield much greater dividends.

The rapid advance in knowledge concerning vitamins and endocrinology has been accompanied by numerous unreliable drugs with their accompanying false claims of usefulness. One has only to turn the pages of certain magazines to see the diverse preparations of the types which are available over the counter of the corner drugstore. The uninformed cannot be relied upon to interpret the meaning of vitamin units, or the potency of glandular preparations, and the various conditions in which their use is indicated. Such advertising is disappearing from the pages of many better magazines.

Fashion dictates are still potent enough to make the manufacture of obesity "cures" very profitable. The danger of these substances containing harmful drugs, such as thyroid and dinitrophenol, has been greatly reduced, so that their main fault now lies in their uselessness.

Although the consumer is often led astray by attractive advertising, clever suggestion, and adroit mishandling of information, there are reliable sources of information concerning such things as drugs, cosmetic preparations, depilatories, obesity cures, laxatives, anti-septics, and numerous other things about which the public is often grossly misinformed. Organizations like the American Medical Association, American Dental Association, American Society for the Control of Cancer, American Heart Association, local, city, county, and state health departments all of which will supply accurate information free of charge or for a very small nominal fee, necessary to defray the expense of printing and mailing materials.

It is a sad reflection upon our mental and emotional stability when we observe how many persons who are in real need of reliable information are either afraid to face the facts of logical reasoning or prefer to think that they will chance upon the right remedy for their ills, in some secret concoction dispensed in a beautiful pink jar. It is highly desirable that nurses recognize the discrepancies which exist between the direct or indirect claims of popularly advertised preparations for the ills and inadequacies of mankind and what these preparations can actually accomplish under even the most desirable of conditions.

Questions for Review

1. State the purpose of the Food and Drug Act.
2. What are the chief provisions of this law?
3. What is the purpose of the Harrison Narcotic Law?
4. Give the chief provisions of this law.
5. Describe the legal control of the manufacture of serums, vaccines, etc.
6. Discuss specific ways in which nurses can help to enforce and respect the requirements of the Harrison Narcotic Law. Discuss the routine procedures in your hospital whereby the narcotic drugs are dispensed, counted, and checked.
7. May any physician who comes to your hospital write an order for a narcotic for his patient?
8. How does the nurse account for narcotic drugs which she may have accidentally contaminated?

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The indiscriminate use of drugs may have several consequences. The contents of the drug may be harmful, and it is well to recall at this point that individuals may have untoward reactions and idiosyncrasies to drugs. Or, the active ingredients of a remedy may not be harmful but they may be entirely useless. Such self-medication may mask symptoms of serious disease and thus delay treatment or render it futile. For example, baking soda and similar common antacids indiscriminately used may relieve the symptoms of gastric ulcer temporarily, but the progress of the disease is not checked. Cancer "cures" are extremely vicious, and the continued use of cathartics may not be without serious consequences. As long as it is possible to obtain medicines without a physician's prescription it will be necessary to continue an educational campaign against "self-medication."

"Patent" medicines are quite generally a waste of money. The discrepancy between their actual cost and the selling price is great. The same amount of money expended for reliable medical care would yield much greater dividends.

The rapid advance in knowledge concerning vitamins and endocrinology has been accompanied by numerous unreliable drugs with their accompanying false claims of usefulness. One has only to turn the pages of certain magazines to see the diverse preparations of the types which are available over the counter of the corner drugstore. The uninformed cannot be relied upon to interpret the meaning of vitamin units, or the potency of glandular preparations, and the various conditions in which their use is indicated. Such advertising is disappearing from the pages of many better magazines.

APPENDIX

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Suggestions for Study

1. Listen to the radio programs over a period of one week. What food, drug, or cosmetic preparations were advertised? What claims were made for the products? Were some claims suggested rather than promised?
2. Bring to class twelve or fifteen examples of drug, cosmetic, or dietary advertisements taken from current magazines. Could the claims made by these advertisements be substantiated by our present scientific knowledge? Be prepared to discuss what seems to you to be good or poor advertising from the standpoint of the legitimacy of the claims.
3. Prepare a list of places from which you may obtain information as to the reliability of drug preparations.
4. What are several organizations which allow their seal of acceptance to be placed on packages of proprietary drug preparations? Compare the significance of these various "seals."

- Liquor Cresolis Saponatus*—Compound solution of cresol, U. S. P. X Saponated solution of cresol
- Lunar Caustic*—Fused silver nitrate
- Lugol's Solution*—Compound iodine solution
- May Apple*—Podophyllin, Mandrake
- Milk of Magnesia*—Magma of magnesia, magnesium hydroxide
- Milk Sugar*—Lactose
- Monkshood*—Aconite
- Sodium*—Sodium
- Neutral Mixture*—Solution of potassium citrate
- Paregoric*—Camphorated Tincture of Opium
- Peruvian Bark*—Cinchona bark—the source of quinine
- Phenacetin*—Acetophenetidin
- Phenazone*—Antipyrine
- Phenol*—Carbolic acid
- Potash*—Crude potassium carbonate or hydrate
- Potassa*—Potassium hydrate
- Precipitated Chalk*—Precipitated calcium carbonate
- Protargin*—Silver proteinate
- Prussian Blue*—Ferric ferrocyanide
- Prussic Acid*—Hydrocyanic acid
- Rochelle Salt*—Sodium and potassium tartrate
- Saccharin*—Benzosulfonide, Gluside
- Salvarsan*—Arsphenamin
- Seidlitz Powders*—Effervescing Rochelle salt
- Smelling Salts*—Ammonium carbonate, some lavender, and a little ammonia

TABLE OF INCOMPATIBILITIES

	ACACIA	ACIDS	ALCOHOL	ALKALIES	ARSENIC	BROMIDES	CALOMEL	CARBONATES	CHLORIDES	CORR. SUBL.	DIGITALIS	IODIDES	IRON SALTS	LEAD SALTS	QUININE	SILVER SALTS	SP. ETH. NIT.	TANNATES	TINCTURES
Acacia.....		+	+										+	+					
Acids.....	+					+													
Alcohol.....		+																	
Alkalies.....			+																
Arsenic.....													+						
Bromides.....			+																
Calomel.....				+									+	+					
Carbonates.....		+																	
Chlorides.....				+											+				
Corr. Subl.....		+		+									+	+	+	+		+	+
Digitalis.....												+	+	+					
Iron salts.....		+								+		+	+					+	+
Iodides.....	+				+		+					+	+			+	+	+	+
Lead salts.....	+					+	+		+	+	+	+				+	+	+	+
Quinine.....																+	+	+	+
Silver salts.....					+											+	+	+	+
Sp. Eth. Nit.....								+					+					+	+
Tannates.....													+	+	+	+			+
Tinctures.....													+	+	+	+			+

Synonymous Terms

- Adrenalin*—Epinephrine
Antifebrin—Acetanilid
Arsphenamin—Salvarsan, 606
Aspirin—Acetylsalicylic acid
Barbital—Barbitone, Veronal
Basham's Mixture—Solution of iron and ammonium acetate
Beeswax—Yellow wax
Benzocaine—Ethyl amido-benzoate
Black Draught—Infusion of senna with magnesium sulfate
Blaud's Pills—Pills of ferrous carbonate
Bleaching Powder—Chlorinated lime
Blue Mass—Mass of mercury
Blue Ointment—Mercurial ointment (dilute)
Brandy—Spiritus Vini Vitis
Brown Mixture—Compound mixture of glycyrrhizae
Blue Vitriol—Copper sulfate
Borax—Sodium borate
Calomel—Mild chloride of mercury
C. C. Pills—Compound pills of calomel
Charcoal—Carbonated wood or organic matter
Collyrium—Eyewash
Corrosive Sublimate—Bichloride of mercury
Dakin's Solution—Mild solution of chlorinated soda
Dichloramine T—Paratoluenesulfondichloramide
Digitalis—Foxglove
Diuretin—Theobromine sodio-salicylate
Dobell's Solution—Liquor sodii boratis compositus
Donovan's Solution—Liquor arseni et hydrargyri iodidi
Dover's Powder—Powder of ipecac and opium
Elaterium—Squirting cucumber
Enteric Pills—Pills coated with salol, keratin, or some substance that will not dissolve in the stomach
Epsom Salt—Magnesium sulfate
Ferruginous Pills—Blaud's pills
Fly Blister—Cantharides plaster
Foxglove—Digitalis
Gaultheria—Wintergreen
Glycyrrhiza—Licorice
Henbane—Stramonium
Hoffmann's Anodyne—Compound spirit of ether
Jimson Weed—Stramonium
Kalium—Potassium
Kumys—Fermented milk of the mare
Labarraque's Solution—Strong solution of chlorinated soda
Lanolin—Hydrated wool fat
Laudanum—Tincture of opium (deodorized)
Limewater—A saturated solution of slaked lime, calcium hydroxide

GLOSSARY

A

- Absorbent.** A medicine or substance which absorbs liquids or other secretion products. Amylum, Carbo Ligni, Gauze, Gossypium Purificatum, Lycopodium, Charcoal.
- Acapnia.** A condition of diminished CO₂ in the blood, with decreased respiration.
- Acidosis.** Condition of decreased alkalinity in the body, caused by excess formation of acid or by depletion of base.
- Acromegaly.** A disease of man, manifested by giantism, due to a tumor of the pituitary gland with increased secretion therefrom.
- Albinism.** A lack of pigment formation indicated by very light hair, pink eyes, a very pale skin.
- Alimentary.** Pertaining to food, or to the digestive apparatus of the body.
- Alterative.** A medicine which changes the processes of the body, thereby re-establishing healthy functions of the system. No specific remedies. Symptomatic measures, diet, vitamins, proper exercise.
- Alveoli.** Small cells or cavities lined with functioning cells.
- Amphibia.** Animals which can live both on land and in water.
- Ampule.** A small glass vial.
- Anaerobic.** Referring to bacteria which thrive in the absence of air (oxygen) and will not grow in the presence of oxygen.
- Analgesic.** A medicine that is used to relieve pain. Acetanilid, Acetyl Salicylic Acid, Acetophenetidin, Antipyrine, Colchicum (gout and rheumatism), Menthol, Opium.
- Anaphrodisiac.** A medicine which decreases sexual desire and function. Belladonna (group), Bromides, Cathartics, Iodides, Opium.
- Anaphylactic.** Pertaining to the increased susceptibility to a foreign protein following a first absorption of the same protein.
- Anchylosed joints.** Bony stiffening of joints, with bone growth.
- Androgen.** A male sex hormone.
- Anemia.** Deficiency of the hemoglobin of the blood.
- Anesthetic (general).** A medicine which produces total loss of consciousness and insensibility to pain. Alcohol, Ether, Chloroform, Nitrogen Monoxide, Ethylene. Loss of sensation.
- Anesthetic (local).** A medicine that diminishes the sensibility of the part to which it is applied. Camphor, Cocaine, Ethyl Chloride, Ether, Novocain, Oil of Allspice, Oil of Clove, Phenol.
- Anhidrotic.** A medicine that decreases the amount of perspiration. Belladonna, Hyoscyamus, Stramonium, Atropine.
- Anodyne (local).** A medicine which when applied locally relieves pain. Aconite, Belladonna Leaves, Belladonna Root, Cannabis, Hyoscyamus, Opium, Stramonium.
- Anoxemia.** Deficiency of oxygen in the blood.

- Soda*—Sodium bicarbonate, cooking soda (cf. washing soda)
Spirit of Nitroglycerin—Glonoin, spirit of glyceryl trinitrate
Stramonium—Jimson weed or Jamestown weed
Sucrose—Sugar, Saccharum
Sweet Spirit of Nitre—Spirit of ethyl nitrite
Tartar Emetic—Antimony and potassium tartrate
Urotropin—Methenamine, Hexamethylenamine
Veronal—Barbital, Barbitone
Vienna Paste—Equal parts of potassa and lime
Washing Soda—Sodium carbonate
Whisky—Spiritus frumenti
White Arsenic—Arsenic trioxide
White Lead—Lead carbonate
Wood Alcohol—Methyl alcohol, Methanol
606—Arsphenamin, Salvarsan

B

- Bacteriology.** The science that studies bacteria and other microorganisms.
- Bacteriophage.** Unknown form of life or substance which destroys bacteria.
- Biochemistry.** A branch of chemistry which studies the chemistry of living matter.
- Bitter (simple).** A medicine which has a bitter taste.
- Aromatic Bitters, Aurantii Amari Cortex, Aurantii Dulcis Cortex, Humulus, Limonis Cortex.
- Bitters.** Calumba, Cinchona, Gentian, Nux Vomica, Quassia, Taraxacum.
- Brachydactylla.** A characteristic lack of the full complement of joints in the fingers or toes; possessing short fingers.

C

- Calcification.** Deposition of lime salts in the tissues.
- Calorie.** A unit of heat used frequently to express the fuel value of food. It is the heat required to raise the temperature of 1 cc. of water 1° C. (from 0° C. to 1° C.). The Calorie ("large calorie") is the heat required to increase the temperature of 1000 grams of water one degree (from 0° to 1°, centigrade scale).
- Carbohydrate.** A class of foods and related products including glucose, cane sugar, starch, cellulose, etc., containing carbon combined with hydrogen and oxygen only. In the best known of these, hydrogen and oxygen are in the ratio of two atoms of hydrogen to every atom of oxygen, as in water, H₂O. Hence the name carbohydrate. Glucose is C₆H₁₂O₆.
- Carcinomatous.** Relating to malignant cancer of epithelial cells.
- Cardiac.** Relating to the heart.
- Cardiac depressant.** A medicine which decreases the heart's action and lowers the blood pressure. Aconitum, Veratrum Viride.
- Dilates the arteries and slows the heart. Amyl Nitrite, Spirit of Nitroglycerin.
- Cardiac stimulants, in toxic doses, are cardiac depressants.
- Cardiac stimulant.** A medicine which increases the heart's action. Alcohol, Ammonia, Caffeine, Camphor (hypodermically), Digitalis, Epinephrine, Pituitary, Adrenalin.
- Carminative.** A medicine which expels gas from the stomach and intestines. Asafoetida, Capsicum, Cardamom Seed, Carum, Caryophyllus, Cinnamonum, Coriander, Fennel, Hops, Mentha Piperita, Zingiber.
- Carotid.** The chief arteries of the head and neck, one on either side.
- Cathartic (purgative).** A medicine which causes evacuation of the bowels by stimulating secretion and by irritation. Calomel, Cascara Sagrada, Fel Bovis, Phenolphthalein, Senna.
- Catheter.** A hollow, flexible tube, used to drain fluid, as from the bladder.
- Cell.** The unit of life; a minute mass of protoplasm with a nucleus, with or without a limiting wall, which has the power of producing other cells and of carrying on other vital processes, such as motion, digestion, secretion, etc.
- Centrifuge.** A device for separating parts by a rapid rotary motion (e.g., cream from milk), which depends on the centrifugal forces of rotary motion.

Antacids. A drug that neutralizes acids. Chalk, Limewater, Magnesia (compounds), Sodium Bicarbonate, Sodium Carbonate.

Anthelmintic. Drug used in the treatment of worms.

Antiemetics. A medicine which stops vomiting.

Local—Atropine, Bismuth Subcarbonate, Bismuth Subnitrate, Cerium Oxalate, Sodium Bicarbonate.

Systemic—Bromides, Codeine, Morphine.

Antigalactagogue. A medicine which decreases the secretion of milk. Belladonna Leaves, Belladonna Root, Hyoscyamus, Stramonium.

Antihysteria. A medicine which relieves hysteria and nervous excitement. Asafoetida, Camphora, Valeriana, Valerianic Acid.

Antineuritic. Pertaining to the property of protecting the nervous system and its parts, as an antineuritic vitamin.

Antipyretic. A medicine which decreases the body temperature. Acetanilid, Acetphenetidin, Aconitum, Antipyrine, Cinchona, Quinine.

Antiscorbutic. Relating to the property of preventing scurvy.

Antiseptic. A medicine which prevents the development of microorganisms.

Antiseptics (stomach). Aromatic Volatile Oils, Phenol Sulfonate, Sodium Salicylate, Sodium Sulfocarbolate.

Antisialogogues. A medicine which decreases the volume of saliva. Belladonna Leaves, Belladonna Root, Hyoscyamus, Stramonium, Atropine.

Antisyphilitic. A medicine used for syphilis. Neocarphenamine, Arsphenamine, Bismuth Salts, Mercury Compounds.

Antitoxin. A chemical (or chemicals) produced by the living body which reacts with and alters to the point of being innocuous, a poison or toxin.

Aphrodisiac. A medicine that stimulates sexual desire and function. Alcohol, Camphor, Cantharides, Nux Vomica, Phosphorus, Strychnine.

Aromatic. A medicine which has a spicy odor and stimulant properties. Anise, Cardamom Seed, Coriander, Fennel, Zingiber.

Arteriole. A small artery.

Arteriosclerosis. Scarring or hardening of arteries as a result of disease in the arterial walls.

Asepsis. Condition of freedom from bacterial contamination. Absence of sepsis.

Astringent. A medicine which contracts tissue and decreases the size of vessels. May be of animal, inorganic or vegetable origin.

Animal. Epinephrine.

Inorganic. Alum, Copper Sulfate, Ferric Chloride, Silver Nitrate, Zinc Sulfate.

Vegetable. Tannin-containing drugs, Galla, Hematoxylin, Kino, Krameria, Quercus, Rheum.

Atonic (or atony). Lack of tone.

Atretic (or atresic). Without a usual opening; imperforate.

Atrophy. Shrinkage and wasting of tissues.

Autocatalytic. The property of a chemical substance, which renders it capable of accelerating its own transformation.

Autolysis. Autodigestion.

Autonomic. Independent in function; self-governing.

- Diaphoretic.** A medicine which increases the secretion of sweat. Ammonium Acetate, Ammonium Citrate, Dover's Powder, Opium, Pilocarpine.
- Digestant.** A medicine which aids digestion. Maltum, Pancreatin, Pepsin, Rennin, HCL.
- Dimorphism.** Occurrence in two different forms. Applies to parts of a plant, such as leaves or flowers, to parts of an animal, or to chemical substances. Thus, crystallized carbon occurs as diamond and as graphite.
- Diphtheria.** A specific infection with the diphtheria bacilli, characterized by marked general poisoning (intoxication) by toxins produced by the bacteria.
- Disinfectant (germicide).** A medicine which destroys microorganisms.
The lay mind makes no distinction between antiseptics and disinfectants.
Antiseptics used in the nose, mouth, and throat—Boric Acid, Camphor, Oil of Cloves, Eucalyptol, Hydrogen Peroxide, Menthol, Oil of Eucalyptus, Silver preparations, Thymol, Oil of Thyme.
Skin Antiseptics. Balsam of Peru, Corrosive Sublimate, Cresols, Dakin's Solution, Ichthyol, Iodine, Iodoform, Phenol, Resina, Salicylic Acid, Solution of Chlorine.
- Diuresis.** Rapid secretion of urine; stimulation of formation of urine.
- Diuretic.** A medicine which increases the quantity of urine secreted.
Direct Action Diuretics. Caffeine Compounds, Water, Salines.
Indirect Action Diuretics by increasing the circulation in the kidney. Digitalis, Squill, Strophanthus.
- Dyspnea.** Difficult or labored breathing.

E

- Ecbolic.** Same as oxytocic or parturient. See below.
- Ectomy.** A word-ending which refers to the excision of a part, as in appendectomy, the excision of the appendix.
- Effluent.** Flowing out.
- Electric potential.** The electric equivalent of the "head" or difference in level of source and outlet of water in a reservoir. The work that can be done by the water is proportional to the product of the "head" and the quantity of water. The work that can be done by electricity is likewise proportional to the difference in electric potential (this is measured in volts) between two points and the quantity of electricity available.
- Embryo.** Early stage of development of an organism, before it is fully formed: as a chick within the egg.
- Emetic.** A substance which causes vomiting.
Local. (Acting on the stomach) Alum, Copper Sulfate, Lukewarm Water, Mustard, Zinc Sulfate.
Systemic. (Acting on the vomiting center in the medulla) Apomorphine, Emetine Hydrochloride, Ipecac, Squill.
- Emmenagogue.** A medicine which aids the function of menstruation. Measures which improve the general health. Iron, Cod Liver Oil, Digitalis, etc., Vitamins.
- Emulsifier.** A substance used to form an emulsion with a fixed oil. Acacia, Tragacanth.
- Endemic.** Habitual, established incidence of disease in a locality.

- Cerebral depressant.** A medicine which decreases the functional activities of the brain. Alcohol (overdose), Anesthetics, Narcotics.
- Cerebral stimulant.** A medicine which increases the functional activity of the brain. Caffeine, Coffee, Kola.
- Cervical.** Referring to the neck of any structure.
- Cholagogue.** A medicine which increases the amount of bile secreted or the amount of bile found in the feces.
 Direct Cholagogues increase secretion of bile. *Fel Bovis*, Sodium Salicylate.
 Indirect Cholagogues increase the amount of bile in the feces by preventing its reabsorption. All cathartics.
- Chorea.** A disease characterized by involuntary muscular spasms—*St. Vitus' dance*.
- Chorionic.** Pertaining to one of the two fetal membranes, the chorion.
- Chromatin.** A substance in the cell nucleus which determines the nature of daughter-cells; the chemical carrier of inheritance in any cell. It is readily stained by dyes (hence the name).
- Chromosome.** Unit of chromatin in the cell nucleus.
- Coalescence.** A growing-together or union.
- Colloid.** A glue-like or gelatinous substance.
- Colloidal Suspension.** A mixture in which particles are held in suspension, such as drops of fat in milk, gas bubbles in foam, etc. The forms and surfaces of the particles change easily with the forces acting on them and are not rigid as in crystals.
- Coloring agents.** *Calendula*, *Coccus*, *Persio*, *Santalum Rubrum*.
- Condiment.** A substance used to make food more appetizing. *Allium*, *Caraway*, *Cinnamon*, *Clove*, *Fennel*, *Ginger*, *Myristica*, *Pimenta*, *Piper*, *Sinapis Nigra*.
- Conjunctivitis.** An inflammation of the mucous membrane of the eyelids.
- Coronary vessels.** Blood vessels of the heart, supplying blood to all parts of the wall.
- Cortex.** The outer portion of a gland or structure; the rind.
- Cystine.** An amino acid which forms one of the components of proteins and contains sulfur.
- Cystitis.** Inflammation of the bladder.
- Cytology.** The science which studies the structure and functions of cells.
- Cytoplasm.** The protoplasm or living substance of a cell outside of its nucleus.

D

- Delirifacient.** A drug which produces delirium. *Cannabis*, *Belladonna*, *Atropine*.
- Demulcent (emollient).** A medicine which protects and soothes the surface to which it is applied. *Acacia*, *Agar*, *Adeps*, *Adeps Lanae*, *Amylum*, *Chondrus*, *Glycyrrhiza*, *Linum*, *Maltum*, *Paraffin*, *Petrolatum*, *Tragacanth*.
- Deodorant.** A medicine or substance which absorbs, masks, or destroys undesirable odors. *Carbo Ligni* (absorbs), *Burning Coffee* and *Fumigators* (masks), *Formalin*, etc.
- Desquamate.** To scale off or peel off (as in the scaling off of the skin in scarlet fever).
- Detergent.** A medicine used as a cleansing agent. *Soaps*, *Tincture of Green Soap*.

G

- Galactagogue.** A medicine which increases the secretion of milk. Fluids, Pituitrin.
- Gene.** The factor or differential substance in a germ cell (or other cell) that determines a given character.
- Genetics.** Genetics is the science which deals with the resemblances and the differences exhibited among organisms related by descent.
- Germinal.** Pertaining to a germ or germ cell.
- Gestation.** Period of pregnancy; phenomena of pregnancy.
- Glomeruli.** Small structures in the kidney composed of capillary blood vessels in a cluster and surrounded by a thin wall.
- Glycemia.** The presence of sugar (glucose) in the blood; hyperglycemia, an excessive amount, hypoglycemia, an unusually low concentration, of sugar in the blood.
- Glycosuria.** Abnormally great secretion of sugar in the urine.
- Gram.** The unit of mass (weight) used in science. A gram is equal to 15.4 grains (apothecary). One ounce (avoirdupois) is equal to 28.4 grams.

H

- Hemolytic.** Pertaining to the property of dissolution of the red blood corpuscles.
- Hepatic.** Relating to the liver.
- Heuristic.** Serving to find out or discover.
- Histology.** The science of the minute structure and function of the tissues of the body; microscopic anatomy and physiology.
- Homozygus.** Breeding true to type.
- Hormone.** A chemical product manufactured by some tissue, such as a gland, which carried by the blood, acts as a messenger and controls other tissues, as by stimulation or depression. Growth, sex characteristics, effects on the heartbeat are instances of such control.
- Hydragogue cathartic (drastic).** A medicine which produces active evacuation of the bowels with watery stools. Gambogia, Colocynthis, Elaterium, Jalap, Podophyllum.
- Hydrogen ion concentration.** Hydrogen ions (H^+) are formed by acids and give acids their acid character; the concentration of these ions in the blood or other liquids has a very vital effect on all life processes.
- Hydrostatic.** Pertaining to the pressure exerted by liquids and on liquids. Medically also: stagnation of fluid.
- Hyperplasia.** Abnormal multiplication of cells; rapid growth.
- Hypersensitive.** Increased sensitiveness.
- Hypertrophy.** Increased size due to growth.
- Hypnotic (somnifacient).** A medicine which induces sleep, closely resembling natural sleep. Barbiturates, Chloral Hydrate, Ethyl Carbamate, Hyoscyamine Hydrochloride, Paraldehyde, Sodium and Potassium Bromide, Sulfonal, Tetronal, Trional.
- Hypophysectomy.** Removal of the hypophysis or pituitary gland, a small gland at the base of the brain.
- Hysteria.** A nervous disease without known pathologic basis.

Endoderm. The innermost layer of cells, e.g., of an embryo.

Enucleate. To remove the nucleus or center.

Enzyme. An organic substance, produced in living cells, that accelerates chemical action. Thus, pepsin, produced by the lining of the stomach, accelerates the digestion (hydrolysis) of proteins.

Epidemic. A widely prevalent disease, as an epidemic of cholera.

Epiphyses. The end portion of long bones, which develops separately from the shaft. *Epiphysis cerebri*: The pineal gland.

Epithellum. A covering surface layer of cells.

Escharotic (caustic). A medicine that chemically destroys the tissue with which it comes in contact. E.g.:

Corrosive Acids:

Inorganic. Hydrochloric, Hydriodic, Hydrofluoric, Nitric, Nitrohydrochloric, Sulfuric.

Organic. Glacial Acetic, Lactic.

Corrosive Alkalies. Ammonium Hydroxide, Potassium Hydroxide, Sodium Hydroxide.

Corrosive Mineral Salts. Mercury Chloride, Zinc Chloride, Silver Nitrate, Mercury Nitrate.

Corrosive Phenols. Creosote, Cresol, Phenol.

Etiology. The science of causes, as of a disease.

Eugenics. The science of improving the human race through its offspring.

Eunuch. An unsexed (castrated) man.

Exacerbation. An increase or aggravation of a process, as a fever, rapid pulse, anemia or pain.

Exophthalmic. Associated with protruding eyeballs.

Expectorant. A medicine which increases or modifies bronchial secretion.

Stimulating Expectorants. Apomorphine, Balsam of Peru, Benzoin, Camphor, Cocillana, Eriodictyon, Ipecac, Nux Vomica, Squill, Tartar Emetic, Terebene, Tolu, Turpentine, Ammonium Chloride.

Sedative Expectorants. Alkalies, Antimony, Lobelia, Prunus Virginiana, Potassium Iodide.

There is no uniformity of opinion as to what are stimulating or what are sedative. The terms refer not to the amount of secretion but to the general effect on the patient. Sedative expectorants usually cause the greatest secretion.

F

Femoral. Relating to the femur or the long bone of the thigh, or to the region of the femur.

Fertilization. The union of a male element (e.g., a spermatozoon in animals, pollen in plants) with the female reproductive cell (the egg or ovum in animals, the ovule in plants), which starts the development of a new individual.

Fetal. Pertaining to the fetus, the young of an animal while still in the womb.

Flavor. A substance or preparation which imparts a distinctive taste to medicines or foods. Cardamom Seed, Coriander Seed, *Rubus Idae Fructus*, Vanilla (most condiments).

M

- Macrophages.** Large white cells of the blood, having the power of ingesting bacteria, débris, etc.
- Malnutrition.** Defective nutrition.
- Mammal.** An animal belonging to the mammalia, the young of which are fed at the breast.
- Matrix.** A mold; the intercellular substance of tissues; the womb.
- Metabolism.** The sum of the chemical processes by which food is used in the body for the development of heat, the doing of work, the formation of new tissues, etc.
- Metamorphosis.** A change of form or structure.
- Miasm.** Injurious exhalations or germs infecting the air.
- Mollusk.** A class of animals, such as oysters, snails, mussels, characterized by protective hard-shell coverings.
- Morbidity.** Degree of sickness; prevalence of sickness.
- Moribund.** In a dying state.
- Morphology.** The science of the form and structure of cells and tissues.
- Motile.** Capable of spontaneous motion.
- Motor paralyzant.** A medicine which paralyzes the motor system.
 General Motor Paralyzants. Conium, Strychnine (toxic doses).
 General Motor Stimulants, in toxic doses, are motor paralyzants.
 Special Motor Stimulants, in toxic doses, are motor paralyzants.
- Motor reflex.** A reflex involving stimulation of a motor nerve; a reflex which produces motion or activity.
- Motor stimulant.** A medicine which increases motor activity.
 General Motor Stimulants. Nux Vomica, Picrotoxin, Caffeine.
 Affecting heart. Cardiac stimulants.
 Affecting respiration. Respiratory stimulants.
 Affecting vessels. Vasoconstrictors and dilators. Oxytocic—hastening parturition.
- Mutation.** An inherited change in the germ plasm, which produces changes in the body.
- Mydriatic.** A medicine which dilates the pupil of the eye. Atropine, Cocaine, Homatropine, Hyoscyamus, Stramonium, Epinephrine.
- Myotic.** A medicine which contracts the pupil of the eye. Physostigmine Salicylate, Pilocarpine Hydrochloride, Pilocarpine Nitrate.
- Myxedema.** A condition of a peculiar swelling of tissues, due to thyroid deficiency and associated with low metabolism and stunted growth and mentality.

N

- Narcotic.** A medicine that produces sleep or stupor and at the same time relieves pain. Cannabis, Codeine, Morphine, Opium.
- Necrosis.** Death of cells or tissues.
- Nerve sedative.** A medicine which allays nervous excitement. Belladonna, Lobelia (bronchial), Tobacco, Hypnotics.
- Nerve stimulants.** Physostigma, Physostigmine Hydrochloride, Pilocarpine, Strychnine, Caffeine.
- Neurasthenia.** Nervous exhaustion.

I

Ileus. Severe colic from intestinal obstruction.

Infundibular. Pertaining to a funnel-shaped passage; applied to the passage of the pituitary extending down from the brain to certain portions of the kidney, part of the nose, etc.

Ingestion. The taking in, e.g., of food.

Interstitial. Structures, such as cells, lying between other structures; a supporting framework of tissue within an organ.

Intestinal antiseptics. Acetyl-Salicylic Acid, Cinchona (quinine), Salol, Charcoal.

Intramuscular. Within, or into, a muscle.

Intravenous. Within, or into, a vein.

Irritant. A medicine which causes irritation.

1. Diluted corrosive acids, alkalies, mineral salts, and phenols.

2. Acids—Arsenous, Formic, Salicylic, Tartaric.

3. Alkali Salts—Potassium Bi-tartrate, Potassium Nitrate, Potassium Sulfate, Sodium Nitrate.

4. Metallic Salts—Antimony and Potassium Tartrate, Copper Sulfate, Iron Chloride, Iron Sulfate, Lead Salts, Mercuric Sulfide.

5. Halogens—Bromine, Chlorine, Fluorine, Iodine.

6. Irritant Gases—Fumes of Ammonia, Hydrochloric Acid, Nitric Acid, Nitric Oxide, Oxides of Sulfur, Sulfurous Acid, Oxides of Phosphorus, Formalin.

7. Vegetable Irritants—Mustard, Capsicum, Croton Oil.

8. Animal Irritants—Cantharides, Sting of Insects.

In Vitro. In artificial conditions, resembling those of life; e.g., in a glass vessel.

In Vivo. In life; in the body. (*In contrast to in vitro.*)

K

Keratinize. To form a hornlike substance; to harden and to thicken, as said of the skin in the formation of a callus, fingernails and horns.

Keratomalacia. Softening of the horny (outer) layer of the skin.

Kilogram. A unit of weight, equal to one thousand grams, or 2.2 pounds avoirdupois.

L

Labile. Unstable, liable to change.

Lacrimal. Pertaining to the tears, tear glands and tear ducts.

Laxative. A medicine which increases evacuation of the bowels. Agar, Castor Oil, Ficus, Petrolatum Liquidum, Prunum.

Lesion. A local abnormality: bruise, wound, scar, inflammation, cavity, etc.

Leucocytes. The white cells of the circulating blood. They are the scavengers and warriors of the blood.

Leucocytosis. Increase (abnormal) in the number of leucocytes.

Leucopenia. Deficiency in the number of leucocytes.

Lithotriptic (antilithic). A medicine which promotes solution of deposits in the urinary tract. Water.

Lockjaw. A disease caused by the tetanus germs, in which the jaws become firmly locked because of muscle spasm.

Lymph. The fluid of the tissues, outside of the blood vessels, having its own circulation and carrying away most of the waste from tissues, later being filtered and poured into the blood.

M

- Macrophages.** Large white cells of the blood, having the power of ingesting bacteria, debris, etc.
- Malnutrition.** Defective nutrition.
- Mammal.** An animal belonging to the mammalia, the young of which are fed at the breast.
- Matrix.** A mold; the intercellular substance of tissues; the womb.
- Metabolism.** The sum of the chemical processes by which food is used in the body for the development of heat, the doing of work, the formation of new tissues, etc.
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Lymph. The fluid of the tissues, outside of the blood vessels, having its own circulation and carrying away most of the waste from tissues, later being filtered and poured into the blood.

- Pericardium.** The membranous sac covering and surrounding the heart.
- Peripheral.** Pertaining to the periphery, outside or boundary. The peripheral nervous system is that outside of the skull and spinal canal.
- Peritoneal.** Pertaining to the membrane lining the abdominal cavity (peritoneum).
- Phagocytosis.** Process of ingestion of larger particles (e.g., bacteria) by cells.
- Pharmacology.** The science which deals with drugs and their effects.
- Photochemistry.** The science which studies chemical changes as affected by light.
- Physiology.** The science which deals with the function of living organisms.
- Piroplasmosis.** Infection by piroplasma, an ovid parasite of the blood, which causes Rocky Mountain spotted fever.
- Placenta.** The structure attaching a fetus to the wall of the uterus, where food passes from the mother's blood to that of the fetus; the afterbirth.
- Planaria.** A group of flatworms.
- Plasma.** The liquid part of blood or lymph.
- Plasmodium.** A microorganism in the blood, causing malaria and similar diseases (*see* piroplasmosis).
- Pleura.** The external lining of the lungs and chest cavity.
- Polarism.** The property of possessing poles (magnetic, electric, cellular, etc.); pertaining to a pole.
- Polyn neuritis.** Inflammation of more than one peripheral nerve; multiple neuritis.
- Pragmatic.** Dealing with causes and effects, with practical consequences.
- Pressor.** Stimulating; increasing tone (e.g., causing an increase in the blood pressure).
- Proliferation.** Growth by multiplication of parts, as in cell division.
- Prophylactic.** Pertaining to prevention of disease.
- Protective.** A medicine which mechanically protects the surface to which it is applied. Adhesive Plaster, Collodion, Paraffin, Yellow Wax, Tannin.
- Proteolytic.** Pertaining to the breaking down of proteins, as in digestion.
- Protoscopically.** Pertaining to inspection of protoplasm.
- Protozoa.** Animal organisms consisting of single cells.
- Pustulant.** A medicine which produces pustules (*pus sacco*), in the openings of the skin glands. Croton Oil.

B

- Rachitic.** Pertaining to rickets.
- Refrigerant.** A medicine which relieves dryness of the mouth and produces a sensation of coolness. Grape Juice, Lemon Juice, Lime Juice, Orange Juice.
- Renal.** Pertaining to the kidneys.
- Respiratory antiseptics.** Medicines used to disinfect the respiratory tract. Benzoin, Creosote, Oil of Turpentine, Pine Tar, Terpin Hydrate, Tolu.
- Respiratory depressant.** A medicine which lowers the activity of the respiratory center and slows respiration. Alcohol, Chloral Hydrate, Chloroform, Codeine, Ether, Hydrocyanic Acid, Ipecac, Opium.
- Respiratory stimulants,** in toxic doses, are respiratory depressants.
- Respiratory stimulant.** A medicine which increases the activity of the respiratory center and accelerates respiration. Ammonia, Apomorphine, Belladonna, Caffeine, Coffee, Strychnine.

Neuralgia. Noninflammatory. Pain along the course of a nerve.

Neuritis. Inflammation of a nerve.

Nucleus. The defined central part of a structure, such as the nucleus of a cell, or of an atom. The portion of a cell necessary for its life and reproduction.

O

Olfactory. Pertaining to the sense and organs of smell.

Ophthalmia. Severe inflammation of the eye.

Oral. Pertaining to a mouth.

Organic matter. Matter similar to that of living material and containing carbon; originally it was erroneously thought that such matter could be produced only by living organisms.

Orthostatic. Pertaining to the position of the body; e.g., horizontal or vertical.

Osteoporosis. Rarefaction of bone by enlargement of its cavities or formation of new spaces.

Ovariectomy. Removal of the ovaries by operation.

Ovogenesis. The origin and development of the ovum or egg.

Oxytocic. Ecboic, parturient. A medicine which hastens childbirth. Ergot, Hypophysis, Quinine, Pitocin, Ergonovine.

P

Parasiticides. Medicines which destroy parasites.

Intestinal Parasites

Anthelmintics. Medicines which destroy or expel intestinal worms.

Ascaricides. Medicines which expel roundworms (*Ascaris Lumbricoides*).

Oil of *Chenopodium*, *Santonin*.

Oxyuricides. Medicines which destroy thread- or pinworms (*Oxyuris Vermicularis*). Infusion of Quassia, and Dilute Oil of Turpentine as rectal injections.

Taenicides. Medicines which destroy tapeworms (of the genera *Taenia*).

Aspidium, *Granatum*, *Pepo*.

Uncinarcides. Medicines which destroy hookworms (*Uncinaria americana*)

Carbon Tetrachloride, Thymol.

Against Skin Parasites

Pediculi (Lice), *Delphinium*, Mercury Preparations, Kerosene.

Ringworm (Tinea species), *Chrysarobin Ointment*, *Formuldehyde*, *Iodine*, *Mercury Preparations*.

Scabies (caused by itch mite), *Balsam of Peru*, *Sulfur Ointment*, *Styrax*.

Parathyroidectomy. Removal of the parathyroid glands; they are located adjacent to the thyroid gland.

Paresis. A paralytic disease of the brain, a late stage of syphilis.

Pari passu. At an equal rate; at an equal pace.

Paroxysm. A sudden, violent outburst.

Parthenogenesis. Reproduction from eggs or ovules without the aid of fertilization by the male element (sperm, pollen).

Pathogenesis. The development of a disease.

Pathology. The science which studies the changes caused by disease.

Pediatrics. The branch of medicine dealing with the diseases of children.

Percutaneous. Through the skin.

Suture. The uniting of parts by stitches (surgery); the line of junction between adjacent parts.

Symptomatology. The combination of symptoms; the symptom complex.

Syndrome. The complete picture of a disease, including all of the symptoms

T

Tactile. By touch.

Therapy. Treatment of disease.

Tonus. The state of continuous partial contraction of a muscle or muscles; tone; tenseness.

Topical. Medically: local (as topical treatment).

Toxic. Poisonous.

Toxicology. The science which deals with poisons.

Trabeculae. Partitions (septa) which extend from the enclosing wall or envelope into the enclosed substance.

Traumatic. Pertaining to physical injury, from a blow, pressure or torsion.

Triturated. Rubbed to a powder.

Tropism. The tendency of living organisms to move or turn in response to an external stimulus (such as a beam of light, an electric charge, etc.).

Tryptic. Pertaining to trypsin, a digestive ferment of the pancreatic juice.

U

Urinary antiseptics. Drugs used to disinfect the urinary tract. Copaiba, Cubeba, Oil of White Sandalwood, Hexamine.

Uterine sedative. A medicine which decreases the functional activity of the uterine system. Bromides, Opium.

Uterine stimulant. A medicine which increases the functional activity of the uterine system. Pituitary Extract, Quinine, Pitocin.

V

Vagus. The tenth pair of nerves from the brain, controlling the heart, lungs, blood vessels, and most of the abdominal organs.

Vascular. Relating to tubes or vessels, such as blood vessels. The vascular system is the system of blood vessels in the body.

Vasoconstriction. Constriction of vessels, such as blood vessels.

Vertebrate. An animal possessing a spinal column; relating to a vertebrate.

Vesicant. A medicine which irritates the skin sufficiently to produce blisters or vesicles. Mustard, Cantharides, Capsicum.

Vibrio. A species of microbes.

Virilism. Masculinity; normal in the male, but a disease in women, characterized by changes in voice, figure, hair, etc.

Viscosity. The property of being viscous or sticky, and which increases the resistance of a fluid or gas to changes of form.

Vulnerary. A medicine employed as a healing agent. Benzoinum, Balsam of Peru, Resina, Antiseptics.

X

Xerophthalmia. A form of degenerative disease of the eye; atrophy of the conjunctiva.

Rubefacient. A medicine which produces a reddening of the skin as a result of dilating the vessels. Mustard, Camphor, Capsicum, Oil of Turpentine, Resina.

S

Saline cathartic. A medicine which causes evacuation of the bowels by increasing secretion and the amount of water in the intestinal tract. Magnesium Sulfate, Sodium Citrate, Sodium Phosphate, Sodium and Potassium Tartrate, Sodium Sulfate.

Seminal. Pertaining to the semen, the sperm, or male reproductive elements.

Senility. The infirmities of old age.

Sequelae. Sequels or after-effects.

Sialogogue. A medicine which increases the amount of saliva. Pilocarpine.
Additional list under Aromatics.

Skeletal. Pertaining to the skeleton.

Sol. A persistent suspension of minute particles in a liquid; a colloidal suspension of solid, liquid or gas particles in a liquid, as in milk, foam, etc.

Somatic. Pertaining to the body, as opposed to the germ plasm.

Spasticity. A tendency to spasm or violent contraction; increased tonus.

Spectrum. The band of colors produced when white light (such as sunlight) is refracted and dispersed by a prism or similar device. The colors of the rainbow represent a spectrum produced by the refraction and dispersion of sunlight by drops of rain.

Sphincters. Ringlike muscles closing an orifice or passage (as in the intestine).

Splanchnic nerve. A large and important nerve in the abdomen, enervating the organs of the abdomen.

Sporadic. Occasional, scattered.

Stereoisomerism. Chemical compounds which have identical composition but different properties are called *isomers*. Stereoisomerism is an isomerism which depends wholly on the arrangement in space of the atoms in the molecules of compounds which have identical composition. The relation of the right to the left hand illustrates one form of such differences in space relationship.

Stereotropic. To see with both eyes; to have focused from both points, as in stereopticon pictures.

Sterile. Unproductive.

Sternutatory. A medicine which causes sneezing. *Phytolacca*, *Quillaja*. Many powdered drugs when inhaled.

Steroid. Like or similar to a sterol.

Sterol. A complex aromatic alcohol, solid at ordinary temperatures (cholesterol).

Stomachic. A medicine which increases the amount of gastric juice or promotes functional activity of the stomach. Alcohol, Pilocarpine, histamine.

Streptococcus. A bacterium, round in shape, and occurring in chainlike arrangement.

Stroma. The framework of an organ or cell; the matrix.

Styptic (hemostatic). A medicine used to check bleeding and hemorrhage.

All of the astringents.

Subcutaneous. Beneath the skin.

Suppurative. Pus producing.

Suprasternal. Above the sternum or breast bone.

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AN INTRODUCTION
TO
MATERIA MEDICA AND PHARMACOLOGY





AN INTRODUCTION TO MATERIA MEDICA AND PHARMACOLOGY

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With 37 Text Illustrations and 15 Color Plates

FIFTH EDITION

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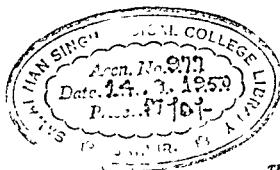
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PREFACE TO THE FIFTH EDITION

The kindly reception of the fourth edition of this book in schools of nursing has afforded an early opportunity for the preparation of the fifth edition.

We have endeavored to make the text suited to the needs of student nurses who are attempting to achieve professional status. This revision has been brought up to date in accordance with the changes in the *United States Pharmacopoeia XIII* and the *National Formulary VIII*. A number of promising new drugs approved by the Council on Pharmacy and Chemistry and included in *New and Nonofficial Remedies* are described. A few preparations which nurses have occasion to administer but which have not yet been approved by the Council are also included.

It is important that students understand that the drugs given today may in a relatively short time be replaced by others or relegated to positions of less importance and also that the older drugs must be periodically reevaluated.

The drug descriptions added to this revision include Benzalkonium Chloride, U. S. P. (Zephiran Chloride); Phemerol Chloride, N. N. R.; Trimethadione, N. N. R. (Tridione); Diphenhydramine Hydrochloride, N. N. R. (Benadryl-Hydrochloride); Pyribenzamine; Streptomycin, N. N. R.; Sulfapyrazine, N. N. R.; Sodium and Potassium Thiocyanate; Folic Acid, N. N. R.; Ethylstibamine, N. N. R.; Dihydroergotamine; Digitoxin, U. S. P. Additional material about Penicillin and the vitamins has also been added.

We would like to express appreciation for the suggestions and continued interest expressed in the present revision by a number of readers and particularly to Mrs. Margaret Staley Cashman, Instructor of Pharmacology at the Sioux Valley Hospital, Sioux Falls, S. D.; Miss Irene Beland, Assistant Professor of Nursing Education at Wayne University; and Miss Jean Dawson, Supervisor of Medical Nursing at St. Mary's Hospital, Rochester, Minn.

E. E. K.

H. A. McG.

PREFACE TO FOURTH EDITION

The publication of the *United States Pharmacopoeia XII* ahead of schedule and the introduction and use of many new and nonofficial

drugs are indicative of the rapid changes which have been taking place in the field of drug therapy. Advancement in this area has been affected by the scientific work done during the recent war and the widespread changes in the treatment of malaria, burns, and tropical diseases.

This edition has been brought up to date with the *United States Pharmacopoeia* XII and it also includes a number of nonofficial preparations which have come into prominent usage.

A number of the chapters have been reorganized and shortened. Others have, to a great extent, been rewritten. Material has been added relative to new chemotherapeutic agents, treatment of burns, vitamin preparations, hormone replacement therapy, and the uses of blood and its constituents.

Several new diagrams have replaced certain illustrations, to make for greater clarity and simplicity. English forms of the names of drug preparations supersede the Latin forms.

The revision of the chapter on chemotherapeutic agents has been the work of Miss Grace Jeanette Blake of St. Mary's School of Nursing. Grateful acknowledgment is made to Miss Jeanne LeGarde of St. Teresa's College, Winona, Minnesota, for the new drawings which were added to this edition. We would also like to record here our appreciation to the members and former member of St. Mary's School of Nursing Faculty, Miss Irene Beland, Miss Evalyne Collins, Sister Mary Brigh and Mrs. Margaret Staley Cashman, for their interest in and suggestions for this revision.

E. E. K.

H. A. McG.

PREFACE TO THIRD EDITION

The rearrangement of content in this edition represents an effort to facilitate the finding of information and to provide for the study of drugs in relation to disease conditions for which they are given. For this reason some chapters on the chemistry of compounds have been omitted entirely or have been incorporated into other chapters of related subject material. Many graphic formulas have been omitted since they are now included in all up-to-date chemistry textbooks. Some new drugs have been added and some forms of therapy have been elaborated upon. Emphasis has been placed upon the responsibilities of nurses and upon their obligation in the prevention of the misuse of drugs.

As the whole field of therapeutics has undergone marked changes, the nurse has come to feel the need of better understanding of scientific principles underlying all treatment. She has been impressed with the fact that if she is to fulfill her function satisfactorily, she must know more about nursing than she did a decade or two ago. The value of learning on the ward and at the bedside of the patient is again being stressed. The suggestions for study both in the classroom and on the ward are given in the hope that the student will utilize opportunities to relate her knowledge of pharmacology to specific nursing activities.

No student can possibly learn even the most essential facts about all the drugs given in her hospital during the time allotted to the formal study of this subject in most schools of nursing. It is hoped, however, that during such a course, she will learn a satisfactory method or technic for studying drugs and that she will develop a growing appreciation for the need of continued study and observation throughout her professional life.

Grateful acknowledgment is made to the following persons for their interest in and suggestions for the revision of this edition: Sister M. Domitilla, Superintendent of St. Mary's Hospital, Rochester, Minnesota; Margaret Staley Cashman, formerly instructor at St. Mary's School of Nursing, as well as present members of the faculty—Miss Irene Beland, Miss Jeanette Blake, and Sister M. Agnella.

E. E. K.

H. A. McG.

PREFACE TO SECOND EDITION

When I was asked to take over the revision of Brodie's *Materia Medica for Nurses*, I did it on one condition only, that I would be allowed to revise, rewrite and revamp the book as I saw fit. The publishers granted this request. The revision appeared under the title *An Introduction to Pharmacology and Materia Medica*.

The rapid exhaustion of a large printing testifies more forcefully than I can to the favorable reception given the book in its new approach to the study of materia medica by undergraduate students in schools of nursing. The action of drugs can be understood only when approached from the animal experimentation standpoint. I have continued to use this approach in the current edition. Every effort has been made to keep this method simple and logical, but the study of drugs and their action is a serious subject. It must be considered by both teacher and student as a matter of moment in the training

of nurses. Much of the nurse's work includes drug administration to patients, and the use of various solutions and antiseptics in hospital routines. Even though drugs and solutions are prescribed under doctors' orders, the nurse in charge of the case should have accurate knowledge of what these drugs will do, why they are administered, and their correct dosage.

It is doubtful whether there is a more important subject in the curriculum of the schools of nursing than materia medica, yet educational directors of these schools have found it one of their greatest teaching problems.

Emphasis has been placed on the most important or useful drugs. Some, like heroin or manganese, because little used, may not be mentioned.

In this edition my son, Robert McGuigan, has rendered valuable assistance. Miss Elsie Krug, St. Mary's Hospital, Rochester, Minn., has been of great service in this revision of the book; having taught this subject for years to undergraduate students she has brought to her task this valuable experience.

HUGH ALISTER MCGUIGAN.

PREFACE TO FIRST EDITION

This book is the outgrowth of an attempt to revise the Fourth Edition of Brodie's *Materia Medica for Nurses*.

The teaching of materia medica is today a matter of grave concern to those who undertake it. Writing a textbook is of even greater moment. Obviously to teach this subject, or to try to teach it, according to the methods followed before the development of pharmacology, is to attempt something that is manifestly unfair both to the student and to the patient who will ultimately come under the student's care.

Knowledge of the physiological and therapeutic action of drugs depends to a great extent upon animal experimentation. Even this method of control has many uncertainties, but the teaching of materia medica and the administration of drugs without the aid afforded by the pharmacological laboratory belongs to a past generation. Much of the material in the fourth edition of Brodie has been retained because it is scientific, sound information, but much new material has been added. The new editions of the *United States Pharmacopoeia* and the *National Formulary* became official June 1, 1936. These

authoritative and fundamental repositories of medicinal drugs render it necessary and obligatory for teachers and students to have a textbook based on this latest revision. I have followed these books in writing this text. In doing this, it has been necessary to leave out many of the older drugs—but at the same time include some new ones. Besides this, new material has been added from the pharmacological and clinical fields. To advocate the use of a drug without such definite information is inexcusable and dangerous. Those who teach materia medica should keep this constantly in mind, and make every effort possible to discredit the use of remedies of unknown therapeutic value. Nothing is more reprehensible than the practice of recommending proprietary medicines that are marketed with no other thought than the profit that will accrue to the manufacturer. The American Medical Association has for years waged warfare against such practice. Every person concerned directly or indirectly with teaching materia medica or who uses drugs for human consumption should support this movement.

I have followed closely in this text the drugs recommended in the *United States Pharmacopoeia* and *National Formulary* and those accepted by the Council of Pharmacy and Chemistry of the American Medical Association. These books should be available to each student.

Illustrations are of great value in teaching; therefore I have used them freely. They will be found closely related to the text. Since the circulatory system and the nervous system are the organs most affected by drugs, I have endeavored to show from experiments on animals just how drugs will affect these two systems, thus eliminating guesswork. Tracings are used that show beyond question what happens when a drug is introduced into the animal body. Its effect on the animal can easily be translated into what it will do when introduced into the human body.

For the convenience of the student, the book is divided into two parts: Part I—Elementary Materia Medica; Part II—Advanced Materia Medica and Therapeutic Application. This arrangement makes the book one of a dual purpose.

Solutions and arithmetic have long been a stumbling block to students of materia medica. To make a mistake in computing the strength of a solution—say bichloride of mercury—is to court disaster, even death. Great pains, therefore, have been taken with this section—endeavoring by checking with the aid of assistants—to make this correct. Administration of drugs is also a matter of extreme importance. This has been given especial attention—using illustrations freely to show just how best to administer drugs.

The frog, dog, cat, and rabbit are man's best friends, offering themselves for experimental purposes. I have endeavored to acquaint the student with this by illustrations. It is difficult, however, for any book to measure up to what the author wants or expects it to do. If this book helps the teacher, eager to teach *materia medica* effectively, and aids the student to understand this subject, I shall be compensated for the time spent. Understanding *materia medica* is no easy task, but it can be mastered by any student willing to work.

We are obligated to the authors of the books referred to in the text, especially the following: Cushny, Sollmann, Meyer-Gottlieb, Jackson, et al.

HUGH ALISTER MCGUIGAN.

Chicago.

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